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RADIATION PROTECTION PROGRAMME 1980 – 1984

**Research priorities
and
Scientific Documentation**

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PREFACE

The Commission of the European Community has prepared a new multiannual research programme in the field of Biology - Health Protection concerning radiation protection and covering the period 1980-1984. This programme proposal has been elaborated in close collaboration with the Advisory Committee on Programme Management "Biology - Health Protection". It has been based on an evaluation of results from the current Radiation Protection Programme, on discussions in study group meetings, on numerous individual contacts with experts and on an analysis of recent publications. Evolution in radiation protection and its concepts has proved the validity of the work undertaken and emphasizes inter alia the importance of risk assessment and of investigations into quantification of effects.

The first part of this booklet contains the official proposal for the framework of the scientific programme as it was transmitted from the Commission to the Council of Ministers. It underlines the priorities derived from the present and foreseeable needs in radiation protection. In order to provide an overall view the research priorities have been grouped into six major sectors : radiation dosimetry and its interpretation, behaviour and control of radionuclides in the environment, short-term somatic, late somatic and genetic effects of ionizing radiation and evaluation of radiation risks.

The second part presents a documentation which is the outcome of the various ways in which the Commission has worked with the scientific community and assembled its views and opinions. As it is published here it should give a detailed insight into the aims of the new Community Radiation Protection Programme and help interested institutions and scientists to prepare research projects and to improve joint planning and coordination. The contributions from each of the scientific areas are presented differently but this in no way reflects priorities as between the various sectors.

BIOLOGY AND HEALTH PROTECTION

Radiation Protection Programme

Proposed Research Activities 1980 - 1984

Excerpt from the proposal of the Commission
to the Council (doc. COM(79) 158 final)

(Original version written in English)

The Radiation Protection Programme Proposal 1980-1984

Proposed research activities

The proposed Radiation Protection Programme of the Community endeavours, through a co-operative European effort, to increase knowledge in radiation protection while taking into account particular problems and skills available in Europe.

The programme will consist of six major activities or sectors which - arbitrarily but conveniently - serve to indicate its overall structure*:

- radiation dosimetry and its interpretation,
- behaviour and control of radionuclides in the environment,
- short-term somatic effects of ionizing radiation,
- late somatic effects of ionizing radiation,
- genetic effects of ionizing radiation,
- evaluation of radiation risks.

The information obtained from previous Commission research programmes and from research conducted elsewhere in the world in comparable fields has been examined, the present state of knowledge reviewed, especially as presented in the UNSCEAR report, future needs for practical protection measures and guidelines have been designed and the necessary research subjects identified.

The programme proposed by the Commission is based on foreseeable requirements of radiation protection in the Community and on the updating and adaptation of the activities already in progress, in the light of the expected development of nuclear facilities and other sources of ionizing radiation and of their possible effects on man and the environment. It is necessary to stimulate research on various subjects which are of crucial importance for the future and proposals to this effect are outlined in the following pages.

* No such subdivision can adequately define the complex scientific content of a balanced radiation protection programme. There is an apparent overlapping between sectors and there are subjects related to all or several of the sectors. Dosimetry, for example, is a basic requirement for all sectors, synergistic effects are observed under many different conditions and the problems of low doses or low dose rates, as well as of the fundamental mechanisms of the observed effects or the need for epidemiological studies manifest themselves in several sectors.

1. Radiation dosimetry and its interpretation

Application of regulations for radiation protection and research on effects of ionizing radiation can only be carried out properly if it is possible to determine absorbed dose and/or other exposure parameters and interpret them in terms of biological effects and the risks to which they give rise. Furthermore the directives of Euratom on Basic Standards require the measurement and recording of certain exposure data which should be carried out in a comparable manner within the Community. Thus the following subjects require further investigation in support of the Radiation Protection Programme as a whole.

- Physical aspects of radiation effectiveness (Microdosimetry)

Biological effects of ionizing radiation are dependent on different irradiation parameters, especially on the radiation quality, interpreted as the spatial and temporal distributions of radiation energy absorption and transfer to biological tissues, the distribution of energy deposition within sensitive sites, as well as the immediate biochemical effects. Despite the considerable progress made in the acquisition of the necessary physical data, more detailed investigations are required to establish convincing relationships between the form of radiation interaction and the dose-effect curves for external radiation and incorporated radio-nuclei. Microdosimetric research on tumour induction and defects of organ function should be able to contribute to the solution of such urgent problems in radiation protection as whether the relative risks from low doses and dose rates of both low and high-LET-radiations have been over or under-estimated, and any changes needed in Quality Factors, with all the impact that such changes might have on shielding design and personal dosimetry.

- Internal dosimetry

Research is needed to develop further quantitative methods to assess the effective radiation dose in the case of incorporation of radioactive isotopes such as tritium and the transuranic elements and the inhalation of radioactive aerosols. The

improvement of dosimetric models used by ICRP for the lung, the gut and the bone, estimation of lung and body content of alpha-emitting radionuclides by whole body counter and excretion measurements respectively, and effects of labelled DNA precursors in the cell nucleus are of particular relevance for radiological protection.

- Dosimetry in case of external irradiation

External irradiation usually gives rise to quite inhomogeneous dose distributions or to partial body irradiation making it sometimes difficult to establish the dose in irradiated organs or tissues under risk. Therefore physical methods have to be improved in order to relate field characteristics of external radiation, such as exposure and quality and differences in tissue densities, more accurately to the organ dose.

- Personal dosimetry and area monitoring

Following the recommendations in recent ICRP publications the revision of radiation protection standards needs to be backed up by research into methods aimed at applying and evaluating these recommendations. The introduction of the effective dose equivalent and the dose equivalent index means that existing measuring methods have to be adapted and conversion factors and functions have to be theoretically and experimentally established for the different quantities, especially as regards instrument calibration.

There are various ways of carrying out personal dosimetry in the individual countries. An analysis will be made of parameters such as internal and external irradiation, contamination, incorporation and excretion which must be determined, in order to make decisions on risk estimates both for acute and chronic exposures and therapeutic measures. Measuring methods will be developed and coordinated. Research is required on protection standards for beta-particles and on the information needed for this purpose. Information from intercomparison programmes and field studies will complement the research results.

- Dosimetry of high-LET-radiation and neutrons

Concerted support is presently necessary to achieve data on high-LET-radiations including neutrons of selected energies of practical importance. Although many physical data and measuring methods for neutrons have been published or elaborated in recent years, completely satisfactory methods in personal neutron dosimetry as well as for neutron and high-LET-dosimetry for radiobiological experiments have yet to be devised. One problem will certainly be to collect and evaluate data that will enable a general consensus to be reached on neutron dosimetry itself. In this area also intercomparisons require a continuing effort, since those which have been carried out have revealed unexpected discrepancies in dosimetry procedures and accuracy.

A programme of continuing development and adaptation for all dosimetric methods - as has taken place in the past - is required to deal with changing needs of radiation protection. For this, some flexibility of approach is needed to tackle mission oriented problems or to carry out exploratory studies of actual needs, or to develop new instruments, thus guaranteeing flexibility and capability for innovation in the future.

- One such problem will be environmental dosimetry. A more realistic estimate should be made of the dose to the public resulting from natural radioactivity and enhanced natural exposure. This forms part of the proper assessment of the risk from man-made radiation sources.
- Another problem of increasing concern is exposure in medical diagnosis. This makes the greatest contribution of any man-made radiation source to the general population. Dosimetric research will aim at reducing the non-essential dose from this exposure while maintaining the quality of the diagnostic information. It will also examine the usefulness of such data for epidemiological studies of radiation effects.

- Still another problem is the possibility of using biological dosimetry for accidents to provide important additional information on the effective dose received. Unfortunately these methods have not proved entirely sufficient in certain accidental situations. Research is needed on the improvement of reliable biological dosimetric methods and on the influence of a wide range of dose rates and non-uniform spatial dose distributions on the biological indicators.

2. Behaviour and control of radionuclides in the environment

The programme of this sector is directed to the acquisition and improvement of data on the behaviour of particular radionuclides in various parts of the environment. Such data are an essential input to assessments of the radiation detriment, in terms of potential harm to health, of routine activities and events (such as accidents) which result in the release of radioactive materials to the environment (see section 4.1.6.). Important subjects, unconnected with nuclear power, which will be included in the programme are those human activities which cause man to be exposed to natural background radiation to an enhanced degree.

The assessment of the detriment requires the estimation of individual and collective doses in the exposed population, usually by means of models which represent the way in which radionuclides are transferred along various and often complex environmental pathways.

In addition, the acquisition of these data will assist those who are responsible for authorizing the discharge of radioactive materials and setting suitable limits for such discharges to the environment and it will also improve the scientific basis of environmental monitoring programmes.

Many data have already been accumulated on the behaviour of several radionuclides in particular sectors of the environment, for example, from studies of fallout from the atmospheric testing of nuclear weapons and from laboratory experiments. However, many gaps remain and many of the data which are available need to be improved in quality.

In the conduct of this programme a reasonable balance between laboratory and field experiments will be necessary; although there is an increasing need for field work to confirm the validity of transfer coefficients derived from laboratory experiments.

Useful information on the reliability of transfer coefficients and on any unexpected sources of contamination might also be derived from data recently collected in several monitoring programmes.

Priority will be given to those radionuclides and environmental pathways which are likely to be important in nuclear power programmes in the coming decades or as a result of radioactive materials that may be introduced into the environment from other sources. In compiling the detailed programme, account will be taken of other Community programmes (see footnote) relevant to nuclear safety and environmental protection thus ensuring that appropriate liaison will be established.

Reviews of existing data and anticipated practices at various stages of the nuclear fuel cycle indicate that the following are important activities in the context of the programme :

- Uranium mining and milling
- uranium enrichment plants
- reprocessing of irradiated fuels
- recycling of uranium and plutonium and the fabrication of mixed-oxide fuels
- the introduction of advanced reactor systems
- the possible introduction of alternative fuel cycles
- decommissioning of nuclear reactors
- the management, including disposal, of the liquid, gaseous and solid wastes that may be generated by all the above activities.

Particular attention will be paid to methods of estimating contamination levels, demarcating contaminated areas and reducing or eliminating radionuclides transfers in accident situations.

Radionuclides which presently appear the most important are the trans-uranic elements and also H-3, C-14, S-35, Kr-85, Tc-99, Ru-106, I-129, I-131 as well as some activation products (Mn-54, Co-60) and natural radioisotopes (radium, thorium and daughter products). The chemical toxicity of some of these nuclides (Tc-99, I-129) must also be considered.

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- Programme on management and storage of radioactive waste
 - Programme on plutonium utilization
 - Programme on uranium exploration and extraction
 - Programme on decommissioning of nuclear power plants
 - Programme on safety of light water reactors.

The main environmental transfer processes requiring further investigation are summarised below :

- resuspension of radionuclides from the sea surface, silts and typical European land surfaces (particularly for Np, Pu, Am and Cm and long lived fission products) ;
- the transfer of radionuclides deposited on the surface of agricultural land to soil, water, plants and animals (particularly for the transuranium nuclides, members of the thorium and radium decay chains and other radionuclides including S-35, Tc-99, Ru-106, I-129).
The way in which the systemic contamination of animals might be influenced by the incorporation of radionuclides in biological materials and by chronic exposure conditions needs special attention ;
- the migration and retention of radionuclides in a range of rocks and soil types typical of Community countries (particularly for the transuranium nuclides and long-lived fission products) ;
- the transfer to sediments of radionuclides released to the aquatic environment, and their possible remobilisation (particularly the transuranium nuclides and long-lived fission products) ;
- the regional distribution and behaviour of long lived radionuclides (e.g. C-14, Tc-99, I-129) with particular reference to their exchange between different sections of the environment (e.g. exchange between the aquatic and terrestrial environments);
- the uptake by aquatic species of particular radionuclides (e.g. Tc-99) where more information is needed ;
- the investigation of possible synergistic effects of radionuclides and conventional pollutants released to the environment, with particular reference to uptake of radionuclides into food chains ;
- the exchange of C-14 and HTO between the atmosphere and terrestrial environment ;
- the atmospheric dispersion and deposition processes in urban areas.

3. Short-term somatic effects of ionizing radiation

Radiation injury occurs at the time of exposure. All subsequent biological effects depend essentially on the rapid changes occurring during an extremely short period of time following the energy absorption. A detailed knowledge of these events would allow to understand the mechanism of the radiation effects.

For many years it has been known that free radicals and their reaction products play an essential role during the early phase of the radiological damage but only recent technological advances made it possible to measure and to identify them in biological material. In relatively few years great progress was made and nowadays, the reaction of radiation-induced free radicals with nucleic acids which are the main biological target of radiation are fairly well known. Further studies in this field, if well coordinated, should give us a clear understanding of the primary mechanism of the radiation damage which would be invaluable for the comprehension and possible control of the consequences of irradiation on living matter.

The study of the early cellular and tissue effects of radiation injury from internal or external origin will be intensified in view of their increasing importance in industry, research and clinical medicine. Lesions which are amenable to treatment include mainly localized radiolesions and damage to the lympho-hemopoietic system. These pathogenic studies will be of basic importance for the development of therapeutic strategies.

Because of the high incidence of acute, subacute or chronic local radiation injuries, the study of their mechanism, prognosis, complications and treatment will be given special attention. Depending on the great variety in the modalities of irradiation, including external as well as internal irradiation (absorption of radioactive material by ingestion, inhalation or wound), they may involve not only the skin but also internal surfaces like those of gastro-intestinal tract, the respiratory tract and many other organs. The connective and vascular tissue which is present almost everywhere in the body deserves particular studies with regard to possible late effects. The high incidence of cancerous transformation following the healing process is

also typical for radiation burns. Therefore, the pathogenesis of these lesions, of the complicating factors and of the mechanism and the kinetics of cellular repopulation will be thoroughly investigated. Also the study will consider the characteristics of antigenic changes and possible neoplastic alterations of the damaged tissue, the role of damage to the immune system and the specific problems encountered when skin-graft therapy is applied.

Early effects of radiation injury to the hemopoietic system by total or subtotal body irradiation and the therapy of those injuries have been studied in previous programmes and considerable progress has been made in understanding and treating the "bone marrow syndrome". However, assessment of the impairment and regeneration potential of the hemopoietic function by existing methods of diagnosis is not yet optimal particularly with regard to the diagnosis of damage to stem cells and to certain populations of lymphocytes. Therefore, the use of chromosomal preparations and other monitors of radiation damage will be studied. As far as therapy is concerned several problems continue to require attention. New radioprotectors have recently been discovered which, if further investigated, could be valuable for human application. Problems of an immunological nature remain a major difficulty, although advances in immunology have greatly improved the feasibility of marrow transplantation in man. These advances include : the removal of immunologically reactive lymphocytes from the marrow suspension (stem cell separation); vastly improved tissue typing and cryopreservation of stem cells (marrow banks) and the feasibility of "manipulating" the immune reactivity which plays a central role in the fate of patients who are treated with a marrow graft (immune-deficiency is the most serious late complication). This part of the research programme will therefore emphasize immunological problems such as :

- a. further improvement of matching for newly discovered tissue antigens;
- b. separation and cryopreservation of stem cells, including a standardized method of assessing their viability;
- c. monitoring and enhancing the immune reactivity of the marrow treated recipient to prevent late complications (infections and possible radiation-induced neoplasia).

4. Late somatic effects of ionizing radiation

Two types of harmful effects may be induced by radiation and some of these may only become manifest long after initial exposure. In one type, involving the so-called "stochastic effects", the frequency with which the effect occurs depends typically upon the size of radiation dose, but the severity of the effects does not in general depend upon the dose. The induction of malignant disease constitutes the most important example of such effects.

In the other type, involving "non-stochastic effects", no significant harm is ordinarily detectable below a certain dose but the severity of the effect which is then produced may vary with the size of the dose. The induction of cataract or of reduced fertility, and the impairment of organ function or blood supply represent changes of this type.

- Induction of stochastic effects

a. Human observations : Malignant changes induced by radiation are of particular importance in regard to radiation protection. The Commission therefore emphasizes the continuing need for assessing the frequency with which different types of malignancy occur in excess of normal expectation in groups of people who have been irradiated (for medical or other reasons) at known dose levels, and have been or can be followed up comprehensively for long periods of time, ideally for several decades, during which further radiation induced tumours may become detectable.

Special attention should be given to dosimetry, length and efficiency of follow up, comparability of the control series, influence of sex, of age at the time of exposure, mortality resulting from radiation-induced tumours, the way in which the latent interval between irradiation and detection of tumours varies with dose or with other factors, the influence of the quality of the radiation (LET), variation of this influence (RBE) with dose, and the form of dose-effect relationship.

Groups of patients who have received repeated or extensive diagnostic radiological investigations will be studied whenever full records such as the frequency of death from malignant disease are obtainable.

Statistical studies of patients who had received internal or external radiotherapy at moderate dosage, particularly in the treatment of non malignant disease should yield additional risk estimates for cancer induction in relevant organs. These results will only be meaningful if control values can be established for the incidence of cancer in patients with the same diseases but who had not been treated by radiation. Such studies should also give some guidance on the safety requirements for these forms of therapy. Similar studies on the effects of radiotherapy for malignant disease, whether given alone or in combination with chemotherapy, could also assist in defining the possible after-effects and the appropriate forms of treatments to minimize the frequency of such hazards. In addition, these studies may throw light on possible synergism between radiation and chemical agents, or a greater sensitivity to radiation carcinogenesis of particular tissues in certain diseases.

- b. Animal studies : in order to elucidate the mechanism of cancer induction, there is an evident need for fundamental experimental studies of the nature of this phenomenon, and of the frequency with which malignant changes are likely to be induced especially by low doses and low dose rates. Such information can form a basis on which valid inferences can be made on the frequency of malignant change to be expected following the even lower doses involved in occupational or other exposure to radiation. Dose effect relationships at low doses, microdosimetric studies, comparison of high and low LET radiation and of dose protraction will be carried out.

Studies concerned with events after incorporation of radionuclides will take into account the following parameters : uptake (by ingestion, or inhalation), radiation quality, biological half life, organ distribution, affinity to particular tissues, inhomogeneity of deposition, metabolism and excretion and studies on the benefit or possible harm of chelating agents.

Special emphasis will also be placed on the variation of factors which are likely to influence the carcinogenic process. These factors include age, sex, hormones, viruses, the immune system and local tissue reactions as endogenous, and some aspects of cocarcinogenesis and synergistic effects as exogenous factors.

The exact identification of the cells at risk and of the early and intermediate sequence of events during carcinogenesis will necessitate the development of new methods (including biochemical and immunological markers). Furthermore, the link between mutagenic and carcinogenic effects should be elucidated.

Standardization of animal experiments, of tumor nomenclature and quantification of morphological endpoints will be continued.

- Induction of non-stochastic effects

In determining the procedures and the dose limits appropriate in radiation protection it is important to know the types of non-stochastic effects which may be induced by radiation in man, the severity of these various effects, and the dose level at which they are liable to be induced. It is particularly important to have information on those effects which might be induced by doses amounting to a few tenths of a sievert each year continued over many years or decades.

This practical requirement applies especially for those tissues or organs in which the rate of fatal cancer induction per unit absorbed dose is likely to be low since for tissues like bone, skin and thyroid the annual dose limit is less likely to be determined by the possible induction of malignancies than by that of harmful non-stochastic changes.

Information will be sought in man and in animals on the total accumulated dose delivered over a substantial proportion of a human or an animal's lifetime which would cause the same effects as are produced by a single dose.

Guidance on these questions needs therefore to be obtained from a review both of effects caused in man and those induced in animals experimentally. In man it is important to survey the dose above which various non-stochastic effects are observed, particularly in the course of radiotherapy at which the appropriate dose levels are reached, but including where possible, the effects of radiation at high LET and those of treatment with radionuclides where relevant. Study of the pathogenesis of these effects is likely to throw light

on the importance of mechanisms of repair.

In this connection it is also necessary to assess the nature of any differences between the reactions of normal and diseased tissues to radiation. In many cases it is to be expected that the accumulated doses which give rise to malignant changes in a tissue will also have caused or initiated non-malignant changes. Any interactions between the development of these two types of effects or the influence of non-malignant changes on the frequency of cancers are important. The examination of the early phase in development of late non-stochastic effects could also prove important for assessing the probability of such late effects.

In relation to the hazard involved in any radiation exposure during pregnancy, teratogenic effects will be studied, particularly with regard to the following : possible existence of a threshold, influence of LET, possible inactivation, recovery or repair of embryonic cells, relationship between damage to single cells of the embryo, major failures in development of the foetus, dose/effects relationship at various stages of embryological development.

The frequencies with which different types of developmental defect (most commonly of the nervous system) are induced by radiation in man and in any experimental model should be as close as possible.

A non-specific shortening of the life span by ionizing radiation still remains uncertain, but its mechanism would call for study if its existence were experimentally proven.

5. Genetic effects of ionizing radiation

The study of radiation effects on genetic material is important because radiations may increase the incidence of chromosomal syndromes and of hereditary diseases and because detailed analyses are required of the complex pathways through which the irradiated cell deals with pre-mutagenic and pre-carcinogenic lesions. Thus, the general objectives in this sector are to provide the information needed for :

- assessing, through the use of the methods currently available (direct estimation method and doubling dose method), the genetic damage induced by radiation in man. The knowledge required for this purpose includes estimates on the birth frequencies of genetic diseases, determination of the values of doubling doses and an evaluation of yields of genetic defects per rad.
- understanding the factors which govern, modify or prevent the establishment of damage. The research carried out in the past now renders possible the genetical and biochemical characterization of some of the processes of DNA repair in human cells. A stimulation of the research on the elucidation of mechanisms may not only allow a continuation of this work but, ultimately, it could provide new means for predicting interactions and effects, for establishing relationships between mutagenesis and carcinogenesis and for preventing or protecting against radiation damages. It should also accelerate the development of methods for the detection of sensitive individuals and, among these, of individuals who are heterozygous for genetic diseases involving a repair deficiency and have an increased sensitivity to mutagens and carcinogens.

For reaching these objectives, in the programme proposed below, emphasis is placed, whenever possible, on the direct analysis of human systems. However, the use of experimental species is maintained in all instances where there is no reliable alternative.

- Assessment and analysis of genetic damages in eukaryotes

The gene mutations and chromosome aberrations which occur spontaneously in man are a source of considerable hardship, being responsible for a substantial fraction of all spontaneous miscarriages and, in full-term survivors, congenital malformations, mental and physical disorders. The incidence of naturally occurring hereditary defects and diseases in human populations has been calculated by UNSCEAR to be approximately 1.0 per cent for dominant and X-linked diseases, 0.1 per cent for recessive diseases, 0.4 per cent for chromosomal diseases and 9.0 per cent for congenital malformations, multifactorial and irregularly inherited conditions. It is thus particularly important, in view of the fact that irradiation is known to induce mutations and chromosomal anomalies, to improve as much as possible the present methods of detection of genetic radiation effects and to establish, through an analysis of the mechanisms of induction, the list of various factors and circumstances which may contribute to an enhancement of incidence rates.

Since human systems are usually not amenable to detailed genetic analyses, a substantial portion of the research effort will be carried out through the use of other eukaryotic material where the similarity of chromosomal organisation (DNA, histones ...) and of cellular organelles implies that many of the induction mechanisms for damage in the nucleus and in the cytoplasm are identical to those of man. The programme involves :

- a) the improvement and development of assay systems and experimental methods with increased resolving power for the detection of induced alterations in both somatic and germ cells of man,
- b) elucidation of the mechanism leading to chromosomal non-disjunction and other aberrations including studies of the relationship between chromosome structure and behaviour (heterochromatin, synaptonemal complex and satellite association).
- c) study of possible associations between radiosensitivity, repair and segregational anomalies,

- d) specific studies on the interactions and relationships between the biological effects of radiation and other environmental agents,
- e) elucidation through a few selected studies, of the effects of irradiation on the mitochondrial genome and its implication for cellular survival.

- Dose-effect relationship

It is particularly difficult to establish the relationship between dose and effect in man because insufficient human data are available and because the quantitative extrapolation of experimental results to man poses serious problems. In view of the importance of dose-effect relationships for the assessment of radiation risk, the programme includes :

- a) epidemiological surveys which focus attention on the relationship between the dose received, the frequencies of aberrations in lymphocytes and the long term biological consequences of the exposure (aplasia in germinal cells and induced effects in live-born and still-born children),
- b) determination of the in vivo kinetics of lymphocytes with the view of facilitating the interpretation of doses from non uniform exposures,
- c) investigations with mammalian experimental species (including primates when possible) designed to collect more data (genetic as well as cytogenetic) which will be useful for quantitative extrapolation of radiation genetic hazards to man,
- d) studies aimed at the appraisal of the methods and assumptions involved in risk assessment in extrapolating from somatic to germ cells and from experimental species to man,
- e) studies on the induction of mutations in germ cells and somatic cells at very low doses and dose-rates and the development of techniques to facilitate such studies.

- Biochemistry and genetics of radiosensitivity and repair

As a consequence to the elucidation, now well in progress, of DNA repair pathways in microorganisms, research involving the use of human cells having mutations leading to repair deficiencies has shown that the mechanisms for repairing DNA damage are of great relevance to human health. Several specific factors affect repair capacities and a number of hereditary diseases that are accompanied by an increased sensitivity to radiation and incidence of cancer are associated with defects in DNA repair.

A large part of the envisaged research is to be executed on mammalian, and particularly human, systems but the use of non-mammalian material will be necessary for the analysis in depth and the modelling of complex biochemical and genetical mechanisms.

The programme will include :

- a) surveying the radiosensitivity of a variety of human cells (fibroblasts, lymphocytes, etc ...) taken from normal "control" group as well as from representatives of those human diseases showing enhanced sensitivity to environmental mutagens. Whenever possible, a detailed analysis of variations in radiosensitivity between individuals will be undertaken,
- b) identification, and genetical and biochemical characterization of variant mammalian cell strains of differing sensitivity and deficient in repair of DNA damage,
- c) investigation of the detailed enzymology of DNA repair pathways (this is best studied at present in microorganisms where formal biochemistry and genetics are well established) and studies of the biochemical specificity and biological significance of DNA lesions in mammalian systems. This will include the use of proteins that recognize specific lesions as analytical probes for monitoring enzymatic repair and the relationship of lesions to mutation, recombination and chromosome aberrations,

- d) studies of mutagenesis and the role of constitutive and inducible repair pathways in mammalian cells. Use will also be made, in this part of the programme, of the several DNA repair deficient mutants recently isolated in Drosophila which provide an opportunity for studying the role of DNA repair pathways in the realization of radiation induced genetic damage in an eukaryotic model system,
- e) analysis of the relationships of DNA repair and related mechanisms to carcinogenesis.

6. Evaluation of radiation risks

Concepts used in radiation protection are liable to be applied in different ways in the Member States. For this reason, it is necessary to attempt to establish common methods for assessing as accurately and objectively as possible the consequences of irradiation for man and his environment. The results of such exercise are also needed for decision making on siting and on choices for energy supply. The new principles of optimization and limitation in radiation protection, which have been recommended in 1977 by ICRP, are based on a risk and detriment concept and require the assessment of realistic relationships between dosimetric quantities and genetic and carcinogenic risks. New dosimetric quantities and concepts have been developed; among them are the effective dose equivalent and the dose equivalent index for the description of individual exposure, and the collective dose and the collective dose commitment for the assessment of the collective health detriment. The practical application of these new terms has to be tested and their relationship to measurable quantities has to be determined.

Three groups of problems must be considered.

The first is the assessment of the individual and collective doses resulting from normal discharge and accidental releases of radioactive substances. This assessment of doses must rely on data obtained by studying the movements of radionuclides in the environment as described under 4.1.2., and should lead to a better determination of the dose distribution among the population and the magnitude of the collective dose taking account with the natural background. Models are required also for any likely pathways of access to man and his environment, and involving the entire nuclear fuel cycle.

As regards optimization in radiation protection which is currently advocated, account must be taken also of all the risks arising from human activities which make use of ionizing radiations or influence irradiation, such as those involving medical applications and technologically enhanced radioactivity. The programme will comprise successive phases of identifying the points to be studied, of assessing the doses received by workers and by the public, and of research

into possible protection measures and their cost.

The second problem is methodological research on the assessment of the detriment. It must make use of data obtained through experimental and epidemiological research described in the relevant sectors of the programme. Two groups of problems should be considered. Firstly, those of the assessment of the detriment in the case of medium and high level irradiation, applicable in the event of an accident. Secondly, those related to low doses, which are particularly relevant for all occupationally exposed persons.

The third problem is the assessment of the economic and social consequences of irradiation. This is a new subject which should be developed in order to establish guidelines for "optimization" of radiation protection activities based on the attainment of "as low as reasonably achievable (ALARA)" levels under conditions which apply in Europe.

BIOLOGI- SUNDHEDSBESKYTTELSE

Program Strålingsbeskyttelse^o

Foreslåede forskningsaktiviteter 1980 - 1984.

Uddrag af forslag fra Kommissionen til Rådet^o
(doc. COM(79) 158 endelig)

(Original udgave på engelsk, dansk oversættelse)

Program "Strålingsbeskyttelse", forslag 1980-1984

Foreslåede forskningsaktiviteter

Det foreslåede program "Strålingsbeskyttelse" for Fællesskabet tilstræber gennem en europæisk samarbejdsindsats at øge viden om strålingsbeskyttelse, idet der tages hensyn til bestemte problemer og den kompetence, der er til rådighed i Europa.

Programmet vil bestå af seks hovedaktiviteter eller sektorer, der - skønmæssigt, men meget passende - kan tjene til at vise dets generelle struktur:*)

- strålingsdosimetri og fortolkning deraf
- radionuklidernes opførsel i miljøet og kontrol med disse
- ioniserende strålings somatiske virkninger på kort sigt
- ioniserende strålings somatiske virkninger på lang sigt
- genetiske virkninger af ioniserende stråling
- vurdering af strålingsrisici.

De data, der er indhøstet ved Kommissionens tidligere forskningsprogrammer og ved forskning udført andetsteds i verden på sammenlignelige områder, er blevet analyseret, vor videns nuværende stade, især som fremlagt i UNSCEAR-rapporten, er blevet gennemgået, fremtidige behov for praktiske beskyttelsesforanstaltninger og vejledninger er blevet udformet og de nødvendige forskningsemner identificeret.

Det program, som Kommissionen foreslår, er baseret på forudselige krav om strålingsbeskyttelse i Fællesskabet og på ajourføring og tilpasning af de allerede igangværende aktiviteter, på baggrund af den forventede udvikling af nukleare faciliteter og andre kilder for ioniserende stråling samt deres mulige indvirkninger på mennesker og miljø. Det er nødvendigt at stimulere forskningen vedrørende forskellige emner, der er af altafgørende betydning for fremtiden, og forslag herom er skitseret på de efterfølgende sider.

*) Ingen opdeling af denne art kan på tilstrækkelig vis definere det komplekse videnskabelige indhold af et afbalanceret program for strålingsbeskyttelse. Der er en tydelig overlapning mellem sektorer, og der er emner, der er beslægtet med alle eller flere sektorer. F.eks. er dosimetri et grundlæggende krav for alle sektorer, synergistiske virkninger iagttages under mange forskellige forhold, og problemerne lave doser eller lave dosisrater, såvel de fundamentale mekanismer i de observerede virkninger eller behovet for epidemiske undersøgelser manifesterer sig i flere sektorer.

1. Strålingsdosimetri og fortolkningen deraf

Anvendelse af bestemmelser for strålingsbeskyttelse og forskning vedrørende virkninger af ioniserende stråling kan kun gennemføres på rette måde, hvis det er muligt at bestemme absorberet dosis og/eller andre eksponeringsparametre og fortolke dem, udtrykt i biologiske virkninger og de risici, de giver anledning til. Endvidere kræver EURATOM's direktiver om grundlæggende normer måling og registrering af visse eksponeringsdata, som skal udføres på sammenlignelig måde inden for Fællesskabet. Derfor kræver efterfølgende emner nærmere undersøgelse til støtte for programmet "Strålingsbeskyttelse" som helhed.

- Fysiske aspekter ved strålingseffektivitet (mikrodosimetri)

Ioniserende strålings biologiske virkninger afhænger af forskellige bestrålingsparametre, især vedrørende strålingskvaliteten, fortolket som fordelingen i tid og rum af strålingsenergiabsorptionen og overførsel til biologiske væv, fordelingen af energiaflejring på følsomme steder såvel som de umiddelbare biokemiske virkninger. Til trods for de betydelige fremskridt, der er gjort i indsamlingen af de nødvendige fysiske data, kræves der mere detaljerede undersøgelser for at fastslå overbevisende sammenhænge mellem formen for strålingsinteraktion og dosis-effekt kurverne for eksternt stråling og inkorporerede radionuklider. Mikrodosimetrisk forskning vedrørende tumorinduktion og defekter i organers funktion skulle kunne bidrage til løsningen af sådanne presserende problemer i strålingsbeskyttelse, som hvorvidt de relative risici hidrørende fra lave doser og dosissrater fra både lave og høje-LET-strålinger er blevet over- eller undervurderet samt alle ændringer, der er påkrævet i kvalitetsfaktorer, med al den indvirkning, som sådanne ændringer vil kunne have på udformningen af afskærmning og persondosimetri.

- Intern dosimetri

Forskning er påkrævet for at udvikle yderligere kvantitative metoder til vurdering af den effektive strålingsdosis med hensyn til inkorporation af radioaktive isotoper såsom tritium og transuraner samt indånding af radioaktive aero-

soler. Forbedring af de dosimetrimoðeller, der af ICRP anvendes for lunger, tarme og knogler, vurdering af lunge- og kropsindhold af alfa-emitterende radionuklider ved henholdsvis helkropstællings- og udskillingsmålinger. Virkningerne af beskrevne DNA-forstadier i cellekernen er ligeledes af særlig relevans for radiologisk beskyttelse.

- Dosimetri i tilfælde af ekstern bestråling

Ekstern bestråling giver sædvanligvis anledning til helt uhomogene dosisfordelinger eller til delkropsbestråling, hvilket undertiden gør det vanskeligt at fastslå dosis i bestrålede organer eller væv, der befinder sig under risiko. Fysiske metoder skal derfor forbedres med henblik på mere præcist at kunne forbinde feltegenskaber af ekstern stråling, såsom eksponering og kvalitet samt forskelle i vævstæthed, med organskade.

- Persondosimetri og områdeovervågning

Efter rekommandationerne i nylige ICRP-publikationer er det nødvendigt, at revisionen af normerne for strålingsbeskyttelse bakes op af forskning i metoder med sigte på at anvende og vurdere disse rekommandationer. Indførelsen af den effektive dosisækvivalent og dosisækvivalentindekset betyder, at eksisterende målemetoder skal tilpasses og omdannelsesfaktorer og -funktioner fastslås teoretisk og eksperimentalt for de forskellige kvantiteter, især med hensyn til kalibrering af instrumenter.

Der findes forskellige måder til udførelse af persondosimetri i de enkelte lande. Der vil blive foretaget analyse af parametre såsom intern og ekstern bestråling, kontaminering, inkorporation og ekskretion, der skal bestemmes for at kunne træffe afgørelser vedrørende risikoskøn, både med hensyn til akutte og kroniske eksponeringer og terapeutiske foranstaltninger. Målemetoder vil blive udviklet og koordineret. Forskning er påkrævet vedrørende beskyttelsesnormer med hensyn til beta-partikler og vedrørende den information, som er nødvendig til dette formål. Information fra programmer for indbyrdes sammenligning og feltstudier vil supplere forskningsresultaterne.

- Dosimetri af høj-LET-stråling og neutroner

Samordnet støtte er i øjeblikket nødvendig for at opnå data vedrørende høj-LET-strålinger, herunder neutroner af udvalgte energier af praktisk betydning. Selv om der i de seneste år er blevet offentliggjort hhv. udarbejdet mange fysiske data og målemetoder for neutroner, må der dog stadig udtænkes fuldstændig tilfredsstillende metoder inden for personneutrondosimetri såvel som inden for neutron- og høj-LET-dosimetri til radiobiologiske eksperimenter. Et problem vil afgjort være at indsamle og vurdere data, der vil gøre det muligt at nå til almindelig enighed om selve neutrondosimetrien. På dette område kræver indbyrdes sammenligninger ligeledes en fortsat indsats, eftersom de sammenligninger, der er blevet foretaget har afsløret uventede afvigelser i dosimetriprocedurer og -nøjagtighed.

Til at imødekomme radiobeskyttelsens skiftende behov kræves et program med fortsat udvikling og tilpasning for alle dosimetri-metoder - således som det hidtil er sket. Hertil kræves en del smidighed i fremgangsmåden for at klare opgavebetonede problemer eller for at udføre udforskende undersøgelser af de faktiske behov, eller at udvikle nye instrumenter for således at garantere smidighed og innovationsevne i fremtiden.

- Et af disse problemer vil blive miljødosimetri. Der bør foretages et mere realistisk skøn over den dosis til befolkningen, der opstår ved naturlig radioaktivitet og forstærket naturlig eksponering. Dette udgør en del af en reel vurdering af risikoen fra menneskeskabte strålingskilder.
- Et andet problem, der trænger sig mere og mere på er eksponering ved medicinsk diagnosticering. Dette udgør den største del af en hvilken som helst menneskeskabt strålingskilde til den almene befolkning. Forskning inden for dosimetri vil sigte mod at nedbringe den ikke-essentielle dosis fra denne eksponering, medens kvaliteten af diagnoseoplysningen bevares. Anvendeligheden af sådanne data til epidemiologiske undersøgelser af strålingens virkninger vil ligeledes blive undersøgt.

- Et andet problem er stadig muligheden for at anvende biologisk dosimetri i forbindelse med ulykker for at skaffe vigtige supplerende oplysninger om den faktisk modtagne dosis. Uheldigvis har disse metoder ikke vist sig at være fuldtud tilstrækkelige i visse uheldssituationer. Der kræves forskning vedrørende forbedring af pålidelige biologiske dosimetrimetoder og vedrørende indflydelsen af en omfattende række dosisstørrelser og ikke-ensartet rumlige dosis-fordelinger på de biologiske indikatorer.

2. Radionuklidernes opførsel i miljøet og kontrollen med disse

Programmet i denne sektor drejer sig om fangst og forbedring af data vedrørende særlige radionuklidernes opførsel i forskellige dele af miljøet. Sådanne data er væsentlige inddata i vurderinger af strålingsskaden, udtrykt som den potentielle sundhedsskade, af rutinevirksomhed og begivenheder (såsom ulykker), der resulterer i udslip af radioaktive materialer til miljøet (jf. 4.1.6.). Vigtige emner, der ikke er forbundet med kernekraft, og som vil blive omfattet af programmet, er de af menneskets aktiviteter, der forårsager, at mennesket bliver udsat for naturlig baggrundsstråling i forstærket grad.

Vurdering af skaden kræver skøn over individuelle og kollektive doser i den bestrålede befolkning, sædvanligvis ved hjælp af modeller, der repræsenterer den måde, hvorpå radionuklider overføres ad forskellige, ofte komplekse veje, i miljøet.

Derudover vil fangst af disse data hjælpe dem, der er ansvarlige for godkendelse af udledninger af radioaktive materialer og fastsættelse af egnede grænser for sådanne udledninger i miljøet, og det vil ligeledes forbedre det videnskabelige grundlag for programmer vedrørende overvågning af miljøet.

Der er allerede blevet samlet mange data om adskillige radionuklidernes opførsel i særlige sektorer i miljøet, f.eks. fra undersøgelser af nedfald fra atmosfærisk afprøvning af nukleare våben og fra laboratorieeksperimenter. Der er imidlertid mange huller endnu, og mange af de data, der er til rådighed, må nødvendigvis forbedres kvalitativt.

Ved udførelsen af dette program vil det være nødvendigt at finde en fornuftig ligevægt mellem laboratorieeksperimenter og eksperimenter i marken; selv om der er et stadig stigende behov for arbejde i marken til at bekræfte gyldigheden af overførselskoefficienter udledt ved laboratorieeksperimenter.

Der vil eventuelt også kunne udledes nyttige oplysninger vedrørende pålideligheden af overførselskoefficienter og en hvilken som helst uventet kontamineringskilde fra de data, der for nylig er blevet indsamlet i forskellige overvågningsprogrammer.

Der vil blive givet prioritet til de radionuklider og veje i miljøet, der kan blive vigtige i kerneenergiprogrammer i de kommende tiår, eller som følge af radioaktive materialer, der eventuelt vil blive udledt i miljøet fra andre kilder. Ved udarbejdelse af det detaljerede program vil der blive taget hensyn til andre fællesskabsprogrammer (jf. fodnote) vedrørende nuklear sikkerhed og miljøbeskyttelse, hvorved det sikres, at der oprettes hensigtsmæssig forbindelse mellem dem.

Gennemgang af eksisterende data og foregrebne anvendelser på forskellige stadier af den nukleare brændselscyklus angiver, at følgende er vigtige aktiviteter i forbindelse med programmet:

- uranudvinding og -knusning
- uranberigningsfabrikker
- oparbejdning af bestrålet brændsel
- behandling af uran og plutonium for fornyet anvendelse og brændselsfremstilling af blandede oxider
- indførelse af avancerede reaktorsystemer
- mulig indførelse af alternative brændselscykler
- nedlukning af kernereaktorer
- forvaltning, herunder bortskaffelse, af flydende, gasformig og fast affald, der måtte opstå ved alle ovennævnte former for virksomhed.

Der vil blive lagt særlig vægt på metoder til vurdering af kontamineringsniveauer, til afgrænsning af kontaminerede områder og til nedbringelse eller eliminering af radionuklidoverførsler ved uheld.

De radionuklider, der i øjeblikket forekommer at være de vigtigste, er transuraner og ligeledes H-3, C-14, S-35, Kr-85, Tc-99, Ru-106, I-129, I-131, såvel som visse aktiveringsprodukter (Mn-54, CO-60) og naturlige radioisotoper (radium, thorium, og heraf afledte produkter). Nogle af disse nuklidens kemiske toksisitet (Tc-99, I-129) bør ligeledes tages i betragtning.

Program for forvaltning og oplagring af radioaktivt affald
Program for behandling af plutonium i letvandsreaktorer for fornyet anvendelse

Program for uranefterforskning og -udvinding
Program for nedlukning af nukleare anlæg
Program for sikkerhed ved letvandsreaktorer.

De væsentligste miljømæssige overførselsprocesser, der kræver yderligere undersøgelse, er sammenfattet nedenfor:

- resuspension af radionuklider fra havoverflade, dyndaflejringer og typiske europæiske landoverflader (især for Np, Pu, Am og Cm og fissionsprodukter med lang levetid);
- overførsel af radionuklider aflejret på overfladen af landbrugsjord til jord, vand, planter og dyr (særlig med hensyn til transurannuklider, led af thorium og radium-henfaldskæder og andre radionuklider, herunder S-35, Tc-99, Ru-106, I-129). Den måde, hvorpå den systematiske kontaminering af dyr kan påvirkes af inkorporering af radionuklider i biologiske materialer og ved kroniske eksponeringsbetingelser, kræver særlig opmærksomhed;
- radionuklidernes vandring og binding i en række bjergarter og jordtyper, der er typiske for Fællesskabets lande (især vedrørende transurannuklider og fissionsprodukter med lang levetid);
- overførsel til aflejringer af radionuklider, der afgives til vandmiljøet, og deres mulige remobilisering (særlig transurannuklider og fissionsprodukter med lang levetid);
- den regionale fordeling og opførsel af radionuklider med lang levetid (f.eks. C-14, Tc-99, I-129) med særlig henvisning til deres udveksling mellem forskellige dele af miljøet (f.eks. udvekslingen mellem vand- og landmiljøer);
- akvatiske arters optagelse af særlige radionuklider (f.eks. Tc-99), hvor der kræves yderligere oplysninger;
- undersøgelse af mulige synergistiske virkninger fra radionuklider og konventionelle forurenende stoffer, der udledes i miljøet, med særlig henvisning til radionuklidernes optagelse i fødekæder;
- udveksling af C-14 og HTO mellem atmosfæren og landmiljøet;
- atmosfæriske sprednings- og aflejringsprocesser i byområder.

3. Ioniserende strålings somatiske virkninger på kort sigt

Strålingslæsioner optræder ved selve eksponeringen. Alle efterfølgende biologiske virkninger afhænger hovedsagelig af de hurtige ændringer, der optræder i et yderst kort tidsrum efter energiabsorptionen. Detaljeret kendskab til disse begivenheder ville gøre det muligt at forstå mekanismen i strålingsvirkninger. I mange år har det været kendt, at frie radikale og deres reaktionsprodukter spiller en væsentlig rolle i den tidlige fase af strålingsskaden, men kun nylige teknologiske fremskridt gjorde det muligt at måle og identificere dem i biologisk materiale. På relativt få år blev der gjort store fremskridt, og nu om dage er der et temmelig godt kendskab til radioinducerede frie radikales reaktion med nukleinsyre, der er det væsentligste biologiske mål for stråling. Yderligere velkoordinerede undersøgelser på dette område skulle give os klar forståelse af strålingsskadens primære mekanisme, der vil blive uvurderlig for forståelsen af og den mulige kontrol med følgerne af stråling for levende stof.

Undersøgelse af tidlige virkninger på celle og væv fra strålingslæsion af intern eller ekstern oprindelse intensiveres på grund af deres stadigt stigende betydning i industrien, forskningen og den kliniske medicin. Læsioner, der kan behandles, omfatter hovedsagelig lokale strålelæsioner og -skade på det lymfomætopoietiske system. Disse patogene undersøgelser vil være af grundlæggende betydning for udviklingen af terapeutiske fremgangsmåder.

På grund af den hyppige forekomst af akutte, sub-akutte eller kroniske lokale stråleskader, vil undersøgelsen af den hermed forbundne mekanisme, prognose, komplikationer og behandling blive helliget særlig opmærksomhed. Afhængig af den store forskelligartethed i de nærmere omstændigheder ved bestråling, herunder ekstern såvel som intern bestråling (optagelse af radioaktivt materiale ved indtagelse, indånding eller gennem sår), kan de berøre ikke blot huden, men også indre overflader såsom mave- og tarmvejene, luftvejene og mange andre organer. Binde- og karvæv, der er til stede næsten over alt i legemet, bør især undersøges med hensyn til mulige senvirkninger. Den hyppige forekomst af kræftomdannelser efter helbredelsesprocessen er ligele-

des typisk for stråleforbrændinger. Derfor vil der blive foretaget en grundig undersøgelse af patogenesen af disse læsioner, af komplikationerne og af mekanismen og kinetikken omkring cel-lerepopulation. Undersøgelsen vil ligeledes behandle karakteristika for antigenændringer og mulige neoplasmaændringer i det beskadigede væg, skadens rolle for det immune system og de særlige problemer, man støder på, når der foretages hudtransplantationer.

Stråleskadens tidlige virkninger på hæmopoiesissystemet ved total eller sub-total legemsbestråling og terapien for disse skader er blevet undersøgt i tidligere programmer, og der er blevet gjort væsentlige fremskridt med hensyn til forståelse og behandling af "knoglemarvssyndromet". Vurderingen af forringelsen og regenereringspotentielt af den bloddannende funktion ved de eksisterende diagnosemetoder er imidlertid endnu ikke optimal, især med hensyn til diagnose af skade på stamceller og på visse lymfosytpopulationer. Derfor vil kromosompræparater og andre overvågere af stråleskade blive undersøgt. For så vidt angår terapi er der adskillige problemer, der fortsat kræver opmærksomhed. Der er for nylig blevet opdaget nye radioprotektorer, der - hvis de yderligere undersøges - kunne blive værdifulde for anvendelse på mennesket. Problemer af immunologisk karakter udgør stadig en af hovedvanskelighederne, selv om fremskridt inden for immunologi har forbedret gennemførligheden af marvtransplantation på mennesket betydeligt. Disse fremskridt omfatter: fjernelse af immunologisk reaktive lymfocytter fra marvsuspensionen (stamcelleseparationen); stærkt forbedret vævs-typebestemmelse og opbevaring ved nedfrysning af stamceller (marvbanks) og gennemførligheden af "manipulering" af den immune reaktivitet, der spiller en central rolle for, hvad der sker med patienter, som behandles med marvtransplantation (mangel på immunitet er den alvorligste senkomplikation). Denne del af forskningsprogrammet vil derfor lægge vægt på immunologiske problemer såsom:

- a. fortsat forbedring af forlidelighed for nyopdagede vævstyper;
- b. separation og opbevarelse ved frysning af stamceller, herunder en standardiseret metode til vurdering af deres levedygtighed;
- c. overvågning og forsøgelse af immunreaktiviteten for den marv-behandlede recipient for at forebygge senkomplikationer (infektioner og mulig neoplasie fremkaldt af stråling).

4. Ioniserende strålings somatiske virkninger på lang sigt

Stråling kan forårsage to typer skadelige virkninger, og nogle af disse viser sig først lang tid efter den oprindelige eksponering. Med hensyn til den ene type, der medfører de såkaldte "stokastiske virkninger", afhænger den hyppighed, hvormed virkningerne optræder, typisk af størrelsen af strålingsdosen, men virkningernes alvorlighed afhænger almindeligvis ikke af dosen. Det vigtigste eksempel på sådanne virkninger er inducering af ondartede sygdomme.

I forbindelse med den anden type, der medfører "ikke-stokastiske virkninger", kan der normalt ikke opdages nogen væsentlig skade under en vis tærskel, men omfanget af den virkning, som så fremkaldes, kan variere med dosens størrelse. Inducering af grå stær eller af reduceret frugtbarhed, og beskadigelse af organfunktioner eller blodforsyning udgør ændringer af denne type.

- Inducering af stokastiske virkninger

a. Observationer af mennesket: Ondartede ændringer induceret ved stråling er af særlig betydning med henblik på strålingsbeskyttelse. Derfor lægger Kommissionen vægt på det fortsatte behov for at vurdere hyppigheden, hvormed forskellige typer ondartethed optræder i større omfang end normalt forventet i persongrupper, som er blevet bestrålet (af medicinske eller andre grunde) ved kendte dosisniveauer, og som er blevet eller kan følges op i udstrakt grad i lange perioder, ideelt i adskillige årtier, i løbet af hvilket yderligere stråleinducerede tumorer måtte blive påviselige.

Der bør lægges særlig vægt på dosimetri, udstrækning og effektivitet af opfølgning, sammenlignelighed af kontrolserier, kønnets og alderens indflydelse ved selve eksponeringen, dødelighed forårsaget af stråleinducerede tumorer, måden hvorpå latente afstande mellem bestråling og detektion af tumorer varierer med dosen eller med andre faktorer, strålingskvalitetens (LET) indflydelse, ændring i denne indflydelse (RBE) med dosen, og formen af dosis/virkning-forholdet. Grupper af patienter, der har gennemgået gentagne eller omfattende diagnostiske radiologiske undersøgelser, vil blive undersøgt, når der kan opnås fuldstændig dokumentation, såsom hyppigheden af dødsfald på grund af ondartet sygdom.

Statistiske undersøgelser af patienter, der havde modtaget intern eller eksternt radioterapi i moderate doser, særlig behandling af godartede sygdomme, skulle give yderligere risikoscenarier for kræftinduktion i relevante organer. Disse resultater vil kunne give mening, hvis der kan opstilles kontrolværdier for kræftforekomst i patienter med samme sygdomme, men som ikke er blevet behandlet med stråling. Sådanne undersøgelser skulle ligeledes give nogle retningslinjer vedrørende sikkerhedskrav for disse former for terapi. Lignende undersøgelser vedrørende virkningerne af radioterapi for ondartede sygdomme, hvadenten den gives alene eller sammen med kemoterapi, kunne ligeledes hjælpe til en definition af mulige eftervirkninger og hensigtsmæssige former for behandling for at minimere hyppigheden af sådanne tilfælde. Derudover kan disse undersøgelser muligvis kaste lys over en mulig synergisme mellem bestråling og kemiske stoffer, eller en større følsomhed over for strålingscarcinogenese af særlige væv ved visse sygdomme.

- b. Dyreundersøgelser: til belysning af kræftinduceringsmekanismen er der et tydeligt behov for fundamentale, eksperimentelle undersøgelser af dette fænomens natur og af hyppigheden, hvormed ondartede ændringer sandsynligvis induceres, særlig ved små doser og lav dosehyppighed. Sådanne oplysninger kan udgøre et grundlag, hvorpå der kan drages gyldige slutninger vedrørende hyppigheden af ondartede ændringer, der må forventes efter de endnu lavere doser, der er involveret i erhvervsmæssig eller anden udsættelse for stråling.

Dosis/virkning-forholdet ved små doser, mikrodosimetriske undersøgelser, sammenligning mellem høj og lav LET-stråling og af doseprotraktion vil blive udført.

Undersøgelser vedrørende begivenheder efter inkorporering af radionuklider vil tage hensyn til følgende parametre: optagelse (ved fordøjelse eller indånding), strålingskvalitet, biologisk halveringstid, organfordeling, affinitet til særlige væv, uensartet aflejring, stofskifte og udskillelse og undersøgelser vedrørende fordelene ved eller den mulige skade af chelater.

Der vil ligeledes blive lagt særlig vægt på den række faktorer, der sandsynligvis kan indvirke på den carcinogenetiske proces. Endogene faktorer omfatter alder, køn, hormoner, vira, immunsystemet og lokale vævreaktioner og eksogene faktorer, og nogle aspekter i carcinogenese og synergistiske virkninger.

Den nøjagtige identificering af de risikoramte celler og af den første og mellemliggende række begivenheder ved carcinogenese vil nødvendiggøre udvikling af nye metoder (herunder biokemiske og immunologiske markører). Desuden bør forbindelsen mellem mutagene og carcinogene virkninger belyses.

Man vil fortsat stadardisere dyreforsøg og tumornomenklatur og kvantificere morfologiske slutpunkter.

- Inducering af ikke-stokastiske virkninger

Ved fastlæggelse af de procedurer og dosisgrænser, der er hensigtsmæssige i strålingsbeskyttelse, er det vigtigt at kende de typer ikke-stokastiske virkninger i mennesket, som kan fremkaldes ved stråling, disse forskellige virkningers omfang, og dosisniveauet, hvorpå de kan induceres. Det er særlig vigtigt, at der findes oplysninger om de virkninger, der eventuelt kan induceres ved doser, der beløber sig til nogle få tiendedele af en sievert hvert år fortsat over mange år eller årtier.

Disse praktiske krav gælder særligt for de væv eller organer, hvori hyppigheden for dødelig kræftinducering pr. enhed absorberet dosis sandsynligvis er lav, eftersom det for væv såsom knogler, hud og skjoldbrusk er mindre sandsynligt, at den årlige dosisgrænse bestemmes af den mulige inducering af ondartetheder end af inducering af skadelige ikke-stokastiske ændringer.

Man vil søge at finde oplysninger i mennesket og i dyr om den totale akkumulerede dosis, der er givet over en væsentlig del af et menneskes eller et dyrs liv, som ville forårsage de samme virkninger, som der frembringes ved en enkelt dosis.

Vejledning i disse spørgsmål skal derfor opnås fra en oversigt over både virkninger forårsaget i mennesket og de virkninger, der induceres i dyr ved eksperimenter. I mennesket er det vigtigt at overvåge den dosis, hvorover der observeres forskellige ikke-stokastiske virkninger, særlig under radioterapi, hvorved de pågældende dosisniveauer opnås, omfattende om muligt virkningerne af stråling ved høj LET og virkningerne af behandling med radionuklider, hvor dette er relevant. Undersøgelse af disse virkninger

patogenese vil sandsynligvis kaste lys over betydningen af reparationsmekanismerne.

I denne forbindelse er det ligeledes nødvendigt at vurdere arten af en hvilken som helst forskel mellem reaktionerne i normale og syge væv over for bestråling. I mange tilfælde kan det forventes, at de akkumulerede doser, der kan forårsage ondartede ændringer i et væv, også vil have forårsaget eller igangsat godartede ændringer. Enhver indbyrdes reaktion mellem udviklingen af disse to typer virkninger eller indvirkningen af godartede ændringer på kræft-hyppigheden er vigtige. Undersøgelsen af det tidlige stadium i udviklingen af ikke-stokastiske senvirkninger kunne ligeledes vise sig at være vigtig for vurdering af sandsynligheden af sådanne senvirkninger.

I forbindelse med den fare, der er ved enhver strålingseksponering under graviditet, vil teratogene virkninger blive undersøgt, særlig med hensyn til følgende: mulig tilstedeværelse af en tærskel, LET's indflydelse, mulig inaktivering, genvinding eller reparation af fosterceller, forholdet mellem skade på enkelte celler i fostret, de største svigt i udviklingen af foetus, dosis/virkning-forholdet på forskellige stadier i fosterudviklingen.

Hyppighederne, hvormed forskellige typer udviklingsdefekter (ofte i nervesystemet) induceres ved stråling i mennesket og i eksperimentelle modeller, bør ligge så nær hinanden som muligt.

En ikke-specifik afkortning af levetiden forårsaget af ioniserende stråling er stadig usikker, men mekanismen heraf burde undersøges, hvis tilstedeværelsen heraf blev påvist eksperimentelt.

5. Genetiske virkninger af ioniserende stråling

Det er vigtigt at undersøge strålingsvirkninger på genetisk materiale, fordi stråling kan øge incidensen af kromosomsyndromer og arvelige sygdomme, og fordi detaljerede analyser af de komplekse processer, hvorved den bestrålede celle håndterer præmutagene og præcarcinogene læsioner, er nødvendige. De generelle mål på dette område er derfor at tilvejebringe den fornødne information til:

- vurdering ved anvendelse af de for tiden disponible metoder (direkte vurderingsmetode og dobbeltdosismetode) af de genetiske skader, der påføres mennesket ved stråling. Den hertil krævede viden omfatter skøn over hyppigheden af genetiske sygdomme ved fødsel, bestemmelse af værdierne for dobbeltdoser og en vurdering af produktionen af genetiske defekter pr. rad.
- forståelse af de faktorer, der styrer, modificerer eller hindrer opståelse af skader. Den hidtil udførte forskning muliggør nu genetisk og biokemisk beskrivelse af nogle af DNA-reparationsprocesserne i humane celler. En stimulering af forskningen vedrørende klarlæggelse af mekanismer kan ikke blot muliggøre en fortsættelse af dette arbejde, men kunne senere resultere i nye midler til forudsigelse af interaktioner og virkninger, konstatering af forbindelser mellem mutagenese og carcinogenese og forhindring af eller beskyttelse mod strålingsskader. Den skulle også fremskynde udviklingen af metoder til påvisning af modtagelige individer, heriblandt af individer, der er heterozygote med hensyn til genetiske sygdomme medførende en reparationsdefekt, og som har øget modtagelighed over for mutagener og carcinogener.

For at nå disse mål lægges der i det nedenfor foreslåede program, når som helst det er muligt, vægt på direkte analyse af humane systemer. Forsøgsarter vil dog stadig blive anvendt i alle tilfælde, hvor der ikke er noget pålideligt alternativ.

- Vurdering og analyse af genetiske skader hos eucaryota

De genmutationer og kromosomaberrationer, der forekommer spontant hos mennesket, er en kilde til megen lidelse, idet de er ansvarlige for en betydelig del af alle spontane aborter og hos overlevende individer medfødte misdannelser og mentale og fysiske lidelser. Incidensen af naturligt forekommende arvelige defekter og sygdomme hos humane populationer er af UNSCEAR beregnet til at være ca. 1,0% for dominante og X-bundne sygdomme, 0,1% for recessive sygdomme, 0,4% for kromosomsygdomme og 9% for medfødte misdannelser, flerkfaktor-tilstande og uregelmæssigt nedarvede tilstande. Efter som stråling vides at fremkalde mutationer og kromosomanomalier, er det derfor særligt vigtigt i videst muligt omfang at forbedre de nuværende metoder til påvisning af genetiske strålingsvirkninger og ved analyse af induceringsmekanismerne at konstatere de forskellige faktorer og omstændigheder, der kan bidrage til en forøgelse af incidensen.

Da humane systemer almindeligvis ikke lader sig anvende til detaljerede genetiske analyser, vil en betydelig del af forskningen blive udført med andet eucaryot materiale, hvor ligheden i kromosomorganisering (DNA, histoner ...) og celleorganeller medfører, at mange af induceringsmekanismerne for skader i kerne og cytoplasma er identiske med menneskets. Programmet omfatter:

- a) forbedring og udvikling af vurderingssystemer og forsøgsmetoder med øget opløsningsevne til påvisning af inducerede ændringer i både somatiske celler og kimceller hos mennesket,
- b) klarlæggelse af den mekanisme, der fører til kromosomal non-disjunction og andre aberrationer, herunder undersøgelser af forbindelsen mellem kromosomstruktur og -opførsel (heterochromatin, synaptinomal kompleks- og satellitforbindelse),
- c) undersøgelse af mulige forbindelser mellem strålingsmodtagelighed, reparation og segregationsanomalier,

- d) specifikke undersøgelser vedrørende vekselvirkningerne og forbindelserne mellem de biologiske virkninger af stråling og andre miljøfaktorer,
- e) klarlæggelse gennem nogle få udvalgte undersøgelser af virkningerne af bestråling på mitochondriegenomet og følgerne for celleoverlevelse.

- Dosis/virkning-forholdet

Det er yderst vanskeligt at fastslå forholdet mellem dosis og virkning hos mennesket, fordi der ikke foreligger nok data om mennesket, og fordi den kvantitative ekstrapolering af forsøgsresultater til mennesket frembyder store problemer. I betragtning af, hvor vigtige dosis/virkning-forholdene er for vurderingen af strålingsrisikoen, omfatter programmet:

- a) epidemiologiske oversigter koncentreret om forholdet mellem den modtagne dosis, hyppigheden af aberrationer i lymfocytterne og de langsigtede biologiske følger af eksponering (aplasi i kimceller og inducerede virkninger hos levendefødte og dødfødte børn),
- b) bestemmelse af lymfocytters in vivo kinetik med henblik på at lette fortolkningen af doser fra ikke-ensartede eksponeringer,
- c) undersøgelser med pattedyrforsøgsarter (om muligt inklusive primater) for at indsamle flere data (genetiske såvel som cytogenetiske) til brug for kvantitativ ekstrapolering af genetiske strålingsrisici til mennesket,
- d) undersøgelser med henblik på vurdering af de metoder og antagelser, der bruges til risikovurdering ved ekstrapolering fra somatiske celler til kimceller og fra forsøgsarter til mennesket,
- e) undersøgelser vedrørende inducering af mutationer i kimceller og somatiske celler ved meget lave doser og dosisniveauer og udvikling af teknikker, der skal lette sådanne undersøgelser.

- Strålingsmodtagelighedens og reparationens biokemi og genetik

Som følge af den klarlæggelse, der nu er godt i gang af DNA-reparationsprocesser i mikroorganismer, har forskning med anvendelse af humane celler med mutationer, der fører til reparationsdefekter, vist, at mekanismerne til reparation af DNA-skader er af stor betydning for den menneskelige sundhed. Flere specifikke faktorer påvirker reparationsevnen, og en række arvelige sygdomme, der ledsages af en øget modtagelighed over for stråling og øget cancerincidens, er forbundet med defekter i DNA-reparationen.

En stor del af den påtænkte forskning skal udføres på pattedyrssystemer, og specielt humane systemer, men det vil blive nødvendigt at anvende ikke-pattedyrmateriale til indgående analyse og modelbeskrivelse af komplekse biokemiske og genetiske mekanismer.

Programmet vil omfatte:

- a) undersøgelse af strålingsmodtageligheden for en række forskellige humane celler (fibroblaster, lymfocytter osv.) taget fra normale "kontrol"-grupper og fra repræsentanter for de menneskelige sygdomme, der viser øget modtagelighed over for miljømæssige mutagener. Når det er muligt, vil der blive foretaget en detaljeret analyse af variationer i strålingsmodtagelighed mellem individer,
- b) identificering og genetisk og biokemisk beskrivelse af varianter af pattedyrcellestammer med forskellig modtagelighed og mangelfulde med hensyn til reparation af DNA-skader,
- c) undersøgelse i enkeltheder af DNA-reparationsprocessernes enzymologi (denne undersøges for tiden bedst hos mikroorganismer, hvor den formelle biokemi og genetik er velkendt) og undersøgelser af den biokemiske specificitet og biologiske betydning af DNA-læsioner i pattedyrssystemer. Dette vil omfatte anvendelse af proteiner, der viser specifikke læsioner, som analytiske prøver til undersøgelser af enzymreparation og forholdet mellem læsioner og mutation, rekombination og kromosomaberrationer,

- d) undersøgelser af mutagenese og konstitutive og inducerbare reparationsprocessers rolle i pattedyrceller. Der vil også i denne del af programmet blive anvendt flere DNA-reparationsdefekte mutanter, som for nylig er isoleret i Drosophila, og som giver mulighed for at undersøge DNA-reparationsprocessers rolle i påvisningen af strålings-induceret genetisk skade i et eucaryot modelsystem,
- e) analyse af forholdet mellem DNA-reparation og beslægtede mekanismer og carcinogenese.

6. Vurdering af strålingsrisici

De begreber, der anvendes inden for strålingsbeskyttelse, vil muligvis blive brugt på forskellig måde i medlemsstaterne. Det er derfor nødvendigt at søge at opstille fælles metoder til så nøjagtigt og objektivt som muligt at vurdere følgerne af bestråling for mennesker og miljø. Resultaterne af et sådant forsøg er også nødvendige for at træffe beslutninger om placering og om valg af energiforsyning. De nye principper for optimering og begrænsning inden for strålingsbeskyttelse, som er blevet anbefalet af ICRP i 1977, er baseret på et risiko- og skadebegreb og kræver vurdering af realistiske forhold mellem dosimetrisk mængde og genetiske og carcinogene risici. Der er udviklet nye dosimetrisk mængde og begreber; heriblandt er det effektive dosisækvivalent og dosisækvivalentindekset til beskrivelse af individuel eksponering og den kollektive dosis og den kollektive dosisforpligtelse til vurdering af den kollektive sundhedsskade. Den praktiske anvendelse af disse nye begreber skal afprøves, og deres forhold til målelige kvantiteter skal bestemmes.

Tre slags problemer må tages i betragtning.

For det første er der vurdering af de individuelle og kollektive doser, der hidrører fra normal udledning og uforsætlige udslip af radioaktive stoffer. Denne dosisvurdering skal bero på data, der er opnået ved studium af radionuklidernes bevægelser i miljøet som beskrevet under 4.1.2., og skulle føre til en bedre bestemmelse af dosisfordelingen blandt befolkningen og størrelsen af den kollektive dosis under hensyntagen til den naturlige baggrund. Det er også påkrævet med modeller for eventuelt mulige adgangsveje til menneske og miljø, og som omfatter hele den nukleare brændselscyklus.

Med hensyn til optimering inden for strålingsbeskyttelse, som for tiden anbefales, må der også tages hensyn til alle de risici, der skyldes menneskelige aktiviteter, hvor der anvendes ioniserende stråling, eller som har indflydelse på bestråling, såsom aktiviteter, der omfatter medicinske anvendelser og teknologisk øget radioaktivitet. Programmet vil omfatte successive faser for identificering af de punkter, der skal undersøges, i vurdering af de doser, arbejdstagerne og offent-

ligheden modtager, og for forskning vedrørende mulige beskyttelsesforanstaltninger samt omkostningerne herved.

Det andet problem er metodologisk forskning vedrørende vurdering af skaden. Hertil skal bruges data erhvervet ved eksperimentel og epidemiologisk forskning beskrevet i de relevante afsnit af dette program. To grupper problemer skal undersøges. For det første problemerne i forbindelse med vurdering af skaden ved middelhøj og høj bestråling i tilfælde af uheld. For det andet problemerne i forbindelse med lave doser, som specielt er relevante for alle erhvervsmæssigt eksponerede personer.

Det tredje problem er vurdering af de økonomiske og sociale følger af bestråling. Dette er et nyt emne, som bør udvikles med henblik på opstilling af retningslinjer for "optimering" af strålingsbeskyttelsesaktiviteter baseret på opnåelse af "as low as reasonably achievable (ALARA)" niveauer, dvs. de laveste rimeligt opnåelige niveauer, under de forhold, der gælder i Europa.

BIOLOGIE - GESUNDHEITSSCHUTZ

Strahlenschutzprogramm

Vorgeschlagene Forschungstätigkeiten 1980 - 1984.

Auszug aus dem Vorschlag der Kommission an
den Rat (Dok. KOM(79) 158 endg.)

(Originalfassung in Englisch, deutsche Übersetzung)

Programmvorschlag "Strahlenschutz" 1980-1984

Aktionsvorschläge

Das vorgeschlagene Strahlenschutzprogramm der Gemeinschaft bemüht sich, durch eine gemeinsame europäische Anstrengung das Wissen auf dem Gebiet des Strahlenschutzes zu erweitern, wobei den besonderen Problemen und Erfahrungen im europäischen Bereich Rechnung getragen werden soll.

Das Programm besteht aus sechs Hauptabschnitten, die mehr oder weniger willkürlich aber zweckorientiert seine Gesamtstruktur aufzeigen sollen*:

- Strahlendosisimetrie und ihre Interpretation,
- Verhalten und Kontrolle der Radionuklide in der Umwelt,
- Somatische Sofortwirkungen ionisierender Strahlung,
- Somatische Spätwirkungen ionisierender Strahlung,
- Genetische Wirkungen ionisierender Strahlung,
- Abschätzung der Strahlenrisiken.

Informationen, die aus früheren Forschungsprogrammen der Gemeinschaft oder aus sonst in der Welt auf vergleichbarem Gebiet durchgeführten Forschungen stammen, wurden überprüft, die derzeitigen Kenntnisse - so wie sie im UNSCEAR-Bericht dargestellt sind - wurden gesichtet, die zukünftigen Anforderungen in Bezug auf praktische Schutzmassnahmen und Leitlinien wurden zusammengestellt und die hierfür notwendigen Forschungsthemen definiert.

Der Programmvorschlag der Kommission ist ausgerichtet auf die vorhersehbaren Erfordernisse des Strahlenschutzes in der Gemeinschaft, die Aktualisierung und Anpassung der bereits laufenden Aktivitäten im Hinblick auf die zu erwartenden Entwicklungen im Bereich des Kernanlagenbaus und anderer Quellen ionisierender Strahlungen sowie auf die möglichen Folgen für den Menschen und die Umwelt. Es ist erforderlich, die Forschungsanstrengungen auf verschiedenen für die Zukunft entscheidend wichtigen Gebieten zu verstärken. Auf den folgenden Seiten wird ein Überblick über die einzelnen Hauptabschnitte des Gesamtvorschlags gegeben.

* Eine solche Unterteilung kann den komplexen, wissenschaftlichen Inhalt eines ausgewogenen Strahlenschutzprogramms nicht wirklich angemessen erfassen. Es gibt deutliche Überschneidungen zwischen einzelnen Abschnitten; ferner gibt es Themen, die zu allen oder mehreren Programmteilen gehören. Dosimetrie z.B. ist in allen Bereichen erforderlich. Synergistische Effekte werden unter vielen verschiedenen Bedingungen beobachtet. Die Probleme der niedrigen Dosen oder Dosisleistungen sowie die der Grundmechanismen der beobachteten Wirkungen und die Notwendigkeit epidemiologischer Untersuchungen spielen in mehreren Abschnitten eine Rolle.

1. Strahlendosimetrie und ihre Interpretation

Die Anwendung der Bestimmungen für den Strahlenschutz und die Untersuchung der Wirkungen ionisierender Strahlung können nur dann korrekt erfolgen, wenn die absorbierte Dosis und/oder andere Bestrahlungsparameter bestimmt und ihre biologischen Wirkungen sowie die durch sie bedingten Risiken interpretiert werden können. Die in den Grundnormen festgelegten Euratom-Richtlinien fordern ausserdem die Messung und Registrierung bestimmter Bestrahlungsdaten, die innerhalb der Gemeinschaft in vergleichbarer Weise durchgeführt werden sollten. Deshalb sind auf den folgenden Gebieten weitere Forschungsarbeiten nötig, um das Strahlenschutzprogramm als Ganzes zu unterstützen.

- Physikalische Aspekte der Strahlenwirkung (Mikrodosimetrie)

Biologische Auswirkungen ionisierender Strahlung sind von verschiedenen Bestrahlungsparametern abhängig, besonders von der Strahlenqualität, die durch die räumliche und zeitliche Verteilung innerhalb empfindlicher Bereiche sowie durch die sofortigen chemischen Effekte beschrieben wird. Obwohl beim Erfassen der notwendigen physikalischen Daten beträchtliche Fortschritte gemacht wurden, sind detaillierte Untersuchungen erforderlich, um die Beziehungen zwischen der Art der Strahlenwirkung und den Dosis-Wirkungskurven bei Bestrahlung von aussen und durch inkorporierte Radionuklide überzeugend darzustellen. Mikrodosimetrische Untersuchungen über die Induktion von Tumoren oder von Defekten der Organfunktionen sollten zur Lösung dringender Probleme des Strahlenschutzes beitragen: ob z.B. die relativen Risiken niedriger Dosen sowohl von Strahlungen niedriger als auch hoher LET über- oder unterschätzt worden sind, ob Qualitätsfaktoren geändert werden müssen mit all den Problemen, die sich durch solche Änderungen für Abschirmplanung und Personendosimetrie ergeben könnten.

- Dosimetrie bei Bestrahlung von innen

Es müssen weitere quantitative Methoden entwickelt werden, um in Fällen einer Inkorporation von radioaktiven Isotopen (z.B. Tritium und Transurane) oder einer Inhalation von radioaktiven Aerosolen die tatsächliche Strahlungsdosis messen zu können. Verbesserungen der von der ICRP verwendeten Dosimetriemodelle für Lunge, Darm und Knochen sowie der Bestimmung des Gehaltes der Lunge und des ge-

santen Körpers an alpha-emittierenden Radionukliden durch Ganzkörperzähler bzw. durch Ausmessen der Exkretion als auch die Untersuchung der Wirkungen markierter DNS-Vorstufen im Zellkern spielen für den Strahlenschutz eine grosse Rolle.

- Dosimetrie bei Bestrahlung von aussen

Bei einer Bestrahlung von aussen ergibt sich gewöhnlich eine ziemlich inhomogene Dosisverteilung oder eine partielle Bestrahlung des Körpers, die die Bestimmung der Dosis in bestrahlten Organen oder gefährdeten Geweben erheblich erschwert. Es müssen daher physikalische Methoden weiterentwickelt werden, um eine klarere Beziehung zwischen Organdosis und Feldcharakteristiken bei Bestrahlung von aussen, wie Exposition, Strahlungsart, Unterschiede in der Gewebedichte, zu erstellen.

- Personendosimetrie und Arbeitsplatzüberwachung

Nach den Empfehlungen in neuesten ICRP-Publikationen bedarf die Revision der Strahlenschutznormen einer Unterstützung durch die Entwicklung von Methoden zur Anwendung und Bewertung dieser Empfehlungen. Die Einführung der effektiven Äquivalentdosis und des Äquivalentdosis-Indexes bedeutet, dass bestehende Messmethoden angepasst und Umrechnungsfaktoren und -funktionen theoretisch und experimentell für die verschiedenen Grössen aufgestellt werden müssen, besonders im Hinblick auf die Eichung der Geräte.

Es gibt in den einzelnen Ländern unterschiedliche Methoden der Personendosimetrie. Es wird eine Analyse von Parametern wie Bestrahlung von innen und von aussen, Kontamination, Inkorporation und Exkretion durchgeführt werden, damit Entscheidungen zu Risikoabschätzungen sowohl bei akuter wie bei chronischer Exposition als auch über therapeutische Massnahmen getroffen werden können. Messmethoden sollen entwickelt und koordiniert werden. Schutznormen für beta-Teilchen und die dazu erforderlichen Informationen sind ein weiterer notwendiger Forschungsteilbereich. Informationen aus Vergleichsprogrammen und Feldstudien werden die Forschungsergebnisse ergänzen.

- Dosimetrie von Strahlung hoher LET und Neutronendosimetrie

Ein konzentriertes Vorgehen ist gegenwärtig nötig, um das Datenmaterial über Strahlungen hoher LET einschliesslich der Neutronen bestimmter praktisch wichtiger Energien zu vervollständigen. Obgleich viele physikalische Daten und Messmethoden für Neutronen in den letzten Jahren veröffentlicht worden sind, müssen wirklich befriedigende Methoden sowohl für die Personendosimetrie bei Neutronenstrahlung als auch für die Neutronen- und Hoch-LET-Dosimetrie bei radiobiologischen Experimenten noch weiter ausgearbeitet werden. Die Zusammenstellung und Bewertung von Daten, die eine allgemeine Übereinstimmung im Bereich der Neutronendosimetrie selbst ermöglichen könnte, stellt sicherlich ein Problem dar. Auch auf diesem Gebiet haben Vergleichsstudien gezeigt, dass weitere Anstrengungen erforderlich sein werden, denn sie haben unerwartete Diskrepanzen bei den Verfahren und bei der Genauigkeit der Dosimetrie aufgezeigt.

Um den sich ändernden Erfordernissen des Strahlenschutzes zu entsprechen, ist ein Programm notwendig, das die Methoden der Dosimetrie stetig weiterentwickelt und anpasst - so wie es bisher bereits geschehen ist. So ist einige Flexibilität erforderlich, um zweckorientierte Probleme zu lösen und notwendige aktuelle Forschungsaufgaben durchzuführen, oder um neue Geräte zu entwickeln und auf diese Weise Flexibilität und Befähigung zur Innovation in der Zukunft zu garantieren.

- Umweltdosimetrie wird ein solches Problem sein. Die Dosis, die der Mensch durch natürliche Radioaktivität und erhöhte natürliche Exposition aufnimmt, sollte realistischer eingeschätzt werden. Dies stellt einen Teil der korrekten Risikoabschätzung für die Gefährdung durch künstliche Strahlenquellen dar.
- Exposition bei der medizinischen Diagnose ist ein weiteres Problem von zunehmendem Interesse. Diese hat den grössten Anteil von allen künstlichen Strahlenquellen an der Strahlenbelastung der Bevölkerung. Dosimetrische Untersuchungen sollen dazu führen, dass die nicht notwendig erforderliche Strahlenbelastung reduziert wird, bei Erhaltung der Qualität der diagnostischen Information. Ausserdem soll die Brauchbarkeit dieser Daten für epidemiologische Untersuchungen der Strahlenwirkungen geprüft werden.

- Die Möglichkeit, die biologische Dosimetrie bei Unfällen einzusetzen, stellt noch ein weiteres solches Problem dar. Mit ihrer Hilfe sollen wichtige, zusätzliche Informationen über die tatsächlich erhaltene Dosis geliefert werden. Leider haben sich diese Methoden in bestimmten Unfallsituationen als nicht wirklich ausreichend herausgestellt. Untersuchungen zur Verbesserung zuverlässiger biologischer Dosimeter sind notwendig. Ausserdem sollen die Einflüsse eines weiten Bereichs der Dosisleistung und einer inhomogenen räumlichen Dosisverteilung auf die biologischen Indikatoren erforscht werden.

2. Verhalten und Kontrolle der Radionuklide in der Umwelt

Das Programm dieses Sektors ist darauf gerichtet, vermehrt Daten zum Verhalten bestimmter Radionuklide in verschiedenen Bereichen der Umwelt zu erfassen. Diese Daten sind wesentlich für eine Beurteilung von Strahlenschäden und einer möglichen Beeinträchtigung der Gesundheit, bei Routinearbeiten sowie bei Ereignissen (z.B. Unfälle), bei denen sich ein Freisetzen radioaktiver Stoffe in die Umwelt ergeben würde (s. Abschnitt 4.1.6.). Ein wichtiges Problem dieses Sektors sind jene Tätigkeiten, die nicht mit der Kernenergie in Verbindung stehen, durch die jedoch der Mensch einer erhöhten natürlichen Grundstrahlung ausgesetzt ist.

Die Beurteilung von Strahlenschäden macht die Abschätzung der kollektiven und individuellen Dosen der exponierten Bevölkerung erforderlich. Dies geschieht gewöhnlich durch Modelle, die den Transfer von Radionukliden über verschiedene und häufig komplizierte Reaktionsfolgen in der Umwelt simulieren.

Eine Erfassung dieser Daten wird auch den Instanzen dienlich sein, die für die Genehmigung der Abgabe radioaktiver Stoffe und für die Festsetzung angemessener Grenzwerte für solche Abgabe in die Umwelt zuständig sind. Ausserdem kann die wissenschaftliche Basis für Umweltüberwachungsprogramme verbessert werden.

Viele Daten zum Verhalten verschiedener Radionuklide in einzelnen Umweltbereichen sind bereits bekannt, z.B. aus Untersuchungen des radioaktiven Niederschlags nach Atomwaffentests in der Atmosphäre und aus Laborexperimenten. Es bestehen jedoch noch zahlreiche Lücken, und viele der vorhandenen Daten bedürfen einer Verbesserung.

Bei der Ausführung dieses Programms müssen Labor- und Feldversuche in einem ausgewogenen Verhältnis zueinander stehen. Allerdings besteht ein ansteigender Bedarf an Feldversuchen, um die Richtigkeit der aus Laborversuchen abgeleiteten Transfer-Koeffizienten zu bestätigen.

Nützliche Informationen über die Zuverlässigkeit von Transfer-Koeffizienten und über mögliche unerwartete Kontaminationsquellen könnten auch aus dem kürzlich gesammelten Datenmaterial von mehreren Überwachungsprogrammen abgeleitet werden.

Besonderer Vorrang wird denjenigen Radionukliden und Reaktionsfolgen in der Umwelt eingeräumt werden, die in Kernenergieprogrammen der kommenden Jahrzehnte, oder die als Folge radioaktiven Materials, das aus anderen Quellen in die Umwelt gelangen könnte, vermutlich grössere Bedeutung erlangen werden. Bei der Zusammenstellung des detaillierten Programms werden andere, die nukleare Sicherheit und den Umweltschutz betreffende Programme der Gemeinschaft (siehe Fussnote) berücksichtigt werden.

Die Überprüfung des bereits vorhandenen Datenmaterials und der voraussehbaren Techniken in den verschiedenen Phasen des Brennstoffkreislaufs ergibt, dass im Zusammenhang mit diesem Programm folgende Aktivitäten wichtig sind:

- Uranbergbau und Uranaufbereitung,
- Urananreicherungsanlagen,
- Wiederaufbereitung bestrahlter Brennstoffe,
- Wiedergewinnung von Uran und Plutonium und Herstellung von Mischoxidbrennstoffen,
- Einführung fortschrittlicher Reaktorsysteme,
- Möglichkeiten der Einführung alternativer Brennstoffkreisläufe,
- Stilllegung von Reaktoren,
- Management und Lagerung der flüssigen, gasförmigen und festen Abfälle, die bei den o.a. Aktivitäten anfallen könnten.

Besondere Aufmerksamkeit wird Methoden gewidmet werden, die bei Unfallsituationen die Abschätzung des Kontaminationsgrades, die Abgrenzung der kontaminierten Gebiete und die Reduzierung oder Eliminierung des Radionuklidtransfers ermöglichen.

Die augenblicklich als wichtigste geltenden Radionuklide sind die Transurane und H-3, C-14, S-35, Kr-85, Tc-99, Ru-106, I-129, I-131 sowie einige Aktivierungsprodukte (Mn-54, Co-60) und natürliche Radioisotope (Radium, Thorium und Tochterprodukte). Hierbei ist auch die chemische Toxizität einiger dieser Nuklide (Tc-99, I-129) in Betracht zu ziehen.

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- Programm "Bewirtschaftung und Lagerung radioaktiver Abfälle".
 - Programm "Verwendung von Plutonium".
 - Programm "Uranschürfung und Urangewinnung".
 - Programm "Stilllegung von Kernkraftwerken".
 - Programm "Sicherheit thermischer Leichtwasserreaktoren".

Die wichtigsten Transferprozesse in die Umwelt, die weitere Untersuchungen erfordern, sind im folgenden zusammengefasst:

- Resuspension von Radionukliden von der Meeresoberfläche, von Sedimenten und typischen europäischen Bodenarten (dies gilt besonders für Np, Pu, Am, Cm und langlebige Zerfallsprodukte);
- Transfer von Radionukliden, die sich auf landwirtschaftlich genutzten Flächen abgelagert haben, in den Boden und in das Wasser, auf Pflanzen und Tiere (dies gilt insbesondere für die Transurane, die Elemente der Thorium- und Radiumzerfallsreihen und andere Radionuklide einschliesslich S-35, Tc-99, Ru-106, I-129). Die Art und Weise, wie die Organkontamination bei Tieren durch die Inkorporation von in biologischem Material enthaltenen Radionukliden sowie durch ständige Exposition beeinflusst wird, erfordert besondere Aufmerksamkeit;
- Die Migration und Retention von Radionukliden in einer Reihe von Gesteinen und Böden, die für die Länder der Gemeinschaft typisch sind (dies gilt besonders für die Transurane und langlebigen Zerfallsprodukte);
- Der Transfer in Sedimente von Radionukliden, die in das aquatische Milieu abgeleitet worden sind und deren mögliche Remobilisierung (dies gilt besonders für Transurane und langlebige Zerfallsprodukte);
- Die regionale Verteilung und das Verhalten von langlebigen Radionukliden (z.B. C-14, Tc-99, I-129), insbesondere im Hinblick auf ihren Übergang zwischen verschiedenen Umweltbereichen (z.B. Übergang zwischen aquatischem und terrestrischem Milieu);
- Die Aufnahme bestimmter Radionuklide (z.B. Tc-99) durch im Wasser lebende Spezies, wozu noch gründlichere Informationen erforderlich sind;
- Die Untersuchung möglicher synergistischer Effekte von Radionukliden und konventionellen, in die Umwelt abgegebenen Schadstoffen, besonders im Hinblick auf die Aufnahme von Radionukliden in Nahrungsketten;
- Der Austausch von C-14 und HTO zwischen Atmosphäre und dem terrestrischen Milieu;
- Dispersion in der Atmosphäre und Vorgänge der Ablagerung in Wohngebieten.

3. Somatische Sofortwirkungen ionisierender Strahlung

Strahlenschäden werden im Augenblick der Exposition induziert. Alle sich daraus ergebenden biologischen Wirkungen hängen im wesentlichen von den schnellen Veränderungen ab, die während eines extrem kurzen, auf die Energieabsorption folgenden Zeitraums auftreten. Eine genaue Kenntnis dieser Vorgänge könnte zu einem Verständnis der Mechanismen der Strahlenwirkungen führen. Es ist bereits seit vielen Jahren bekannt, dass freie Radikale und ihre Reaktionsprodukte während der Frühphase der Strahlenschädigung eine entscheidende Rolle spielen. Es ist jedoch erst durch neuere technologische Entwicklungen möglich geworden, diese in biologischem Material zu messen und zu bestimmen. In nur wenigen Jahren sind grosse Fortschritte erzielt worden. Heute sind die Reaktionen von strahleninduzierten, freien Radikalen mit Nukleinsäuren - den Strahlungen gegenüber anfälligstem biologischen Material - ziemlich gut bekannt. Weitere Untersuchungen auf diesem Gebiet sollten - bei guter Koordinierung - ein klares Bild der primären Mechanismen der Strahlenschädigungen ergeben. Diese könnten zum Verständnis und zu Möglichkeiten der Kontrolle der Folgen einer Bestrahlung von lebendem Material genutzt werden.

Untersuchungen früher schädigender Wirkungen auf Zellen und Gewebe durch Strahlung von innen oder von aussen werden in Anbetracht ihrer wachsenden Bedeutung in Industrie, Forschung und klinischer Medizin intensiviert. Die einer Behandlung zugänglichen, krankhaften Veränderungen umfassen in der Hauptsache lokalisierte Strahlenverletzungen und -schäden des Lympho-hämatopoietischen Systems. Diese pathogenetischen Untersuchungen werden für die Entwicklung therapeutischer Behandlungsmethoden von grundlegender Bedeutung sein.

Da akute, subakute oder chronische lokale Strahlenschäden häufig auftreten, wird den Untersuchungen ihrer Mechanismen, ihrer Prognose, ihrer Komplikationen und ihrer Behandlung besondere Aufmerksamkeit gewidmet werden. Aufgrund der Vielfalt der Bestrahlungsmodalitäten - einschliesslich der Bestrahlung von aussen und von innen (Absorption radioaktiven Materials durch Nahrungsaufnahme, Einatmung oder Verletzung) - müssen sie sich nicht nur auf die Haut, sondern auch auf tieferliegende Oberflächen wie die des Darmtrakts, der Atemwege und vieler anderer Organe erstrecken. Dem konnektiven und vaskulären Gewebe, das sich praktisch überall im Körper befindet, sind besondere Untersuchungen im Hinblick auf mögliche Spätwirkungen vorbehalten.

Das häufige Auftreten krebsartiger Veränderungen nach dem Heilungsprozess ist ebenfalls typisch für Strahlenverbrennungen. Daher werden die Pathogenese dieser Verletzungen, der erschwerenden Faktoren, des Mechanismus und der Kinetik zellulärer Repopulation eingehend untersucht. Die Untersuchung befasst sich ausserdem mit den typischen Kennzeichen der Antigenveränderungen, der möglichen neoplastischen Veränderungen des geschädigten Gewebes, mit der Rolle, die eine Schädigung des Immunsystems spielt, sowie mit spezifischen Problemen, die bei Anwendung der Therapie mit Hauttransplantationen auftreten.

Frühwirkungen der Strahlenverletzungen auf das blutbildende System bei totaler oder teilweiser Körperbestrahlung sowie die Therapie solcher Verletzungen sind bereits in früheren Programmen untersucht worden. Zum Verständnis und zur Behandlung des "Knochenmarksyndroms" sind beträchtliche Fortschritte erzielt worden. Allerdings ist die Beurteilung der Schädigung und des Regenerationspotentials der blutbildenden Funktionen mit den vorhandenen diagnostischen Methoden - insbesondere im Hinblick auf Schädigungen der Stammzellen bestimmter Lymphozytenpopulationen - noch nicht optimal. Daher soll der Einsatz von Chromosomenindikatoren und anderen Kontrollmöglichkeiten für Strahlenschäden untersucht werden. Was die Therapie anbetrifft, so erfordern verschiedene Probleme weiter grosse Aufmerksamkeit. Erst vor kurzem wurden neue Radioprotektoren entdeckt, die bei weiterer Untersuchung für eine Anwendung beim Menschen in Frage kommen könnten. Die immunologischen Probleme stellen immer noch eine der Hauptschwierigkeiten dar, obwohl Fortschritte in der Immunforschung die Möglichkeiten der Knochenmarktransplantation beim Menschen wesentlich verbessert haben: Immunologisch reaktive Lymphozyten können aus der Knochenmarksuspension entfernt werden (Stammzellenseparation); Gewebecharakterisierung und Gefrierkonservierung der Stammzellen (Knochenmarkbanken) wurden verbessert; die Immunreaktionsfähigkeit, die für die mit Knochenmarktransplantation behandelten Patienten eine zentrale Rolle spielt (Immunschwäche ist die schwerwiegendste Spätfolge), kann manipuliert werden. In diesem Teil des Forschungsprogramms werden daher immunologische Probleme folgenden Inhalts besonders betont werden:

- a) Weitere Verbesserung des Nachweises neu entdeckter Gewebeantigene,
- b) Separation und Gefrierkonservierung von Stammzellen, einschliesslich einer standardisierten Methode, für die Bestimmung ihrer Lebensfähigkeit,

- c) Überwachung und Stärkung der Immunreaktionsfähigkeit des Knochenmarkempfängers zur Vorbeugung gegen Spätfolgen (Infektionen, Möglichkeit strahleninduzierter Tumore).

4. Somatische Spätwirkungen ionisierender Strahlung

Zwei Arten von schädigenden Wirkungen können durch Strahlung induziert werden; einige davon können erst lange nach der ersten Exposition in Erscheinung treten. Bei dem einen Typ, der die sogenannten "stochastischen" Wirkungen umfasst, hängt die Häufigkeit, mit der die Wirkung auftritt, von der Höhe der Strahlendosis ab; die Schwere der Wirkung ist im allgemeinen jedoch nicht von der Dosis abhängig. Das wichtigste Beispiel für eine solche Wirkung ist die Induzierung maligner Krankheiten.

Bei dem anderen Typ, der die "nicht-stochastischen" Wirkungen umfasst, kann im allgemeinen bis zu einer gewissen Dosis kein signifikanter Schaden nachgewiesen werden, die Schwere der dann auftretenden Wirkung kann jedoch mit der Höhe der Dosis variieren. Die Induzierung des grauen Stars oder einer verminderten Fruchtbarkeit, die Schwächung der Organfunktionen oder der Blutbildung sind Veränderungen dieses Typs.

- Induzierung stochastischer Wirkungen

- a) Beobachtungen am Menschen: Durch Strahlen induzierte maligne Veränderungen haben im Strahlenschutz besondere Bedeutung. Die Kommission betont daher die weiterhin bestehende Notwendigkeit, die Häufigkeit der verschiedenen Typen maligner Veränderungen bei Gruppen zu bestimmen, die mit einer bekannten Dosis bestrahlt werden (aus medizinischen oder anderen Gründen) und die über lange Zeiträume hinweg umfassend beobachtet werden können, und festzustellen, ob sie höher liegt als es den normalen Erwartungen entspräche. Der ideale Beobachtungszeitraum umfasst mehrere Jahrzehnte, während derer weitere strahleninduzierte Tumore nachweisbar werden könnten.

Besondere Aufmerksamkeit sollte gerichtet werden auf die Dosimetrie, auf Dauer und Aussagekraft von follow-up-Studien, die Vergleichbarkeit von Kontrollserien, den Einfluss von Geschlecht, Alter, Expositionszeit, die durch strahleninduzierte Tumore verursachte Sterblichkeit, die mit der Dosis oder anderen Faktoren variierende Latenzzeit zwischen Bestrahlung und Nachweis von Tumoren, den Einfluss der Strahlenqualität (LET), die

dosisabhängige Veränderung dieses Einflusses (RBE) und die Art der Dosis/Wirkung-Beziehung.

Gruppen von Patienten, die wiederholten oder umfangreichen radiologischen diagnostischen Untersuchungen ausgesetzt waren, werden immer dann überprüft, wenn vollständige Protokolle, z.B. zur Häufigkeit des Todes durch maligne Krankheiten, verfügbar sind.

Statistische Erhebungen an Patienten, die bei der Behandlung nicht maligner Krankheiten mittleren Strahlendosen von innen oder aussen ausgesetzt waren, sollten zusätzliche Werte für die Abschätzung des Risikos der Krebsinduzierung in relevante Organe erbringen. Diese Erhebungen haben nur dann einen Sinn, wenn Kontrollwerte über die Anzahl der Krebserkrankungen von Patienten, die an derselben Krankheit litten, aber nicht bestrahlt wurden, erstellt werden können. Diese Untersuchungen sollten ausserdem einige Anleitung zu den Sicherheitsanforderungen bei diesen Therapiemethoden erbringen. Ähnliche Studien zur Bestrahlungstherapie bei malignen Erkrankungen - sei es diese Therapie allein oder in Verbindung mit einer Chemotherapie - könnten ebenfalls dazu beitragen, die möglichen Folgewirkungen und die geeignete Behandlung zu definieren, um die Häufigkeit dieser Schäden auf ein Mindestmass zu reduzieren. Ausserdem könnten diese Arbeiten einen möglichen Synergismus von Strahlung und chemischen Substanzen oder eine grössere Anfälligkeit bestimmter Gewebe bei bestimmten Krankheiten gegen die durch Strahlen hervorgerufene Karzinogenese aufzeigen.

- b) Untersuchungen an Tieren: Um den Mechanismus der Krebsinduktion klären zu können, sind grundlegende, experimentelle Arbeiten zur Natur dieses Phänomens und zur Häufigkeit, mit der maligne Veränderungen besonders durch niedrige Dosen und niedrige Dosisleistung wahrscheinlich induziert werden, erforderlich. Solche Informationen können eine Grundlage schaffen, von der aus auf die Häufigkeit geschlossen werden kann, mit der maligne Veränderungen als Folge der noch niedrigeren Dosen erwartet werden müssen, die bei berufsbedingter oder anderer Strahlenexposition auftreten. Hierzu werden Dosis/Wirkung-Beziehungen bei niedrigen Dosen, mikrodosimetrische Untersuchungen sowie der Vergleich von Strahlungen hoher und niedriger LET und der Dosisprotraktion durchgeführt werden. In Untersuchungen, die die Vorgänge nach einer Inkorporation von Radionukliden betreffen, werden folgende Parameter berücksichtigt: Aufnahme (durch Nahrungsaufnahme oder Einatmen), Strahlenqualität, biologische Halbwertszeit, Verteilung auf die Organe, Affinität zu bestimmten Geweben, Inhomogenität der Ablagerung, Stoffwechsel und Ausscheidung, ferner Unter-

suchungen über den Nutzen oder möglichen Schaden chelatbildender Substanzen.

Besondere Aufmerksamkeit wird der Veränderung der Faktoren beigemessen, die den karzinogenen Prozess wahrscheinlich beeinflussen. Diese Faktoren sind endogen - wie Alter, Geschlecht, Hormone, Viren, Immunsystem und lokale Gewebereaktionen - sowie exogen - wie einige Aspekte der Kokarzinogenese und synergistische Effekte.

Die exakte Identifizierung gefährdeter Zellen sowie früher und intermediärer Abläufe von Vorgängen während der Karzinogenese erfordert die Entwicklung neuer Methoden (einschliesslich biochemischer und immunologischer Marker). Ausserdem sollten die Zusammenhänge zwischen mutagenen und kanzerogenen Wirkungen geklärt werden.

Die Standardisierung der Tierversuche, der Tumornomenklatur und die quantitative Bestimmung der morphologischen Endstadien wird fortgesetzt.

- Induzierung nicht-stochastischer Wirkungen

Wenn angemessene Verfahren und Dosis-Höchstwerte für den Strahlenschutz festgelegt werden sollen, ist es wichtig, die Formen nicht-stochastischer Wirkungen zu kennen, die durch Strahlung beim Menschen induziert werden können. Ausserdem müssen die Schwere dieser verschiedenen Effekte und die Dosishöhe, bei denen sie mit Sicherheit induziert werden, bekannt sein. Es ist besonders wichtig, Informationen über solche Wirkungen zu erhalten, die durch Dosen hervorgerufen werden, die sich auf einige Zehntel eines Sievert pro Jahr belaufen und dies während vieler Jahre oder Jahrzehnte.

Diese praktische Voraussetzung gilt besonders für die Gewebe oder Organe, in denen die Krebsinduzierungsquote pro absorbierte Doseinheit wahrscheinlich niedrig ist, während die jährliche Höchstdosis für Gewebe wie Knochen, Haut und Schilddrüse weniger über eine mögliche Induzierung maligner Erkrankungen zu bestimmen ist als über die von schädlichen nicht-stochastischen Veränderungen.

An Menschen und Tieren werden Daten gesucht werden, über die gesamte akkumulierte Dosis, die verteilt über einen längeren Zeitraum des menschlichen oder tierischen Lebens verabreicht wurde und die dieselben Wirkungen zeigt wie jene, die durch eine einzige Dosis hervorgerufen werden.

Zur Lösung dieser Fragen ist daher eine Überprüfung sowohl der Wirkungen beim Menschen als auch der experimentell bei Tieren induzierten Wirkungen notwendig. Beim Menschen ist es wichtig, die Dosis zu untersuchen, oberhalb der verschiedene nicht-stochastische Effekte beobachtet werden. Dies

gilt besonders im Verlauf der Strahlentherapie, bei der entsprechende Dosiswerte erreicht werden. Wo es möglich ist, sollen jedoch auch die Strahlenwirkungen bei hoher LET und die Auswirkungen nach Radionuklidtherapie beobachtet werden. Untersuchungen der Pathogenese dieser Wirkungen werden wahrscheinlich die Bedeutung der Reparationsmechanismen klären.

In diesem Zusammenhang ist es ferner erforderlich, die Unterschiede zwischen den Reaktionen normaler und kranker Gewebe auf Bestrahlung zu erfassen. In vielen Fällen kann erwartet werden, dass die akkumulierte Dosis, die zu malignen Veränderungen in einem Gewebe führt, ausserdem auch nicht maligne Veränderungen hervorgerufen oder initiiert hat. Alle Wechselwirkungen zwischen der Entwicklung dieser beiden Wirkungsarten ebenso wie der Einfluss nicht maligner Veränderungen auf die Häufigkeit der Krebserkrankungen sind wichtig. Die Untersuchung des frühen Entwicklungsstadiums von späten, nicht-stochastischen Wirkungen könnte sich ebenfalls für die Beurteilung der Wahrscheinlichkeit solcher Spätwirkungen als relevant herausstellen.

Im Hinblick auf Gefahren durch Bestrahlung während der Schwangerschaft müssen teratogene Wirkungen speziell auf folgende Detailfragen hin untersucht werden: mögliches Vorhandensein eines Schwellenwertes, Einfluss der LET, mögliche Inaktivierung, Erholung oder Wiederherstellung embryonaler Zellen, Beziehungen zwischen der Schädigung von Einzelzellen des Embryos, grössere Störungen in der Entwicklung des Fötus und Dosis/Wirkung-Verhältnis in verschiedenen Stadien der embryonalen Entwicklung.

Die Häufigkeitsraten der unterschiedlichen Formen von Entwicklungsdefekten (meistens des Nervensystems) durch Strahleninduktion beim Menschen und bei jeder Art experimenteller Modelle sollten weitgehendst übereinstimmen.

Eine nicht-spezifische Verkürzung der Lebenszeit durch ionisierende Strahlungen ist noch ungewiss, sollten die experimentellen Arbeiten diesbezüglich Hinweise erbringen, so wären die entsprechenden Mechanismen zu untersuchen.

5. Genetische Wirkungen ionisierender Strahlung

Eine Untersuchung der Strahlenwirkungen auf genetisches Material ist wichtig, weil Strahlung zu einem erhöhten Auftreten chromosomaler Defekte und zu Erbkrankheiten führen kann und weil detaillierte Analysen der komplizierten Reaktionsfolgen erforderlich sind, mit denen die bestrahlten Zellen prämutagene oder präkanzerogene Schädigungen verarbeiten. Die Hauptaufgaben dieses Sektors bestehen darin, Informationen zu folgenden Problemen zu liefern:

- Bewertung der durch Strahlung verursachten genetischen Schäden beim Menschen mit Hilfe der gängigen Methoden (direkte Messung und Methode der Verdoppelungsdosis). Um hier zu Ergebnissen zu gelangen, müssen Messungen der Häufigkeit von Geburten mit Erbkrankheiten, Bestimmung der Werte der Verdoppelungsdosen und Messungen der auftretenden genetischen Defekte pro rad durchgeführt werden.
- Verständnis der Faktoren, die das Auftreten der Schädigung steuern oder verhindern. Die bisher durchgeführte Forschung ermöglicht es heute, einige der Vorgänge der DNS-Reparation in menschlichen Zellen genetisch und biochemisch zu beschreiben. Die Forschung zur Klärung der Mechanismen anzuregen, würde nicht nur bedeuten, dass diese Arbeiten fortgesetzt würden, sondern es könnten letztlich neue Möglichkeiten gefunden werden, Wechselwirkungen und Effekte vorauszusagen, Beziehungen zwischen Mutagenese und Karzinogenese zu erfassen und Strahlenschäden vorzubeugen oder davor zu schützen. Ausserdem sollten Methoden beschleunigt entwickelt werden, durch die sensitive Individuen nachgewiesen werden könnten und darunter solche, die für Erbkrankheiten heterozygot sind, wodurch eine Reparationschwäche gegeben ist, und die gegenüber mutagenen und karzinogenen Faktoren erhöht anfällig sind.

Um diese Ziele zu erreichen, liegt in dem im folgenden vorgeschlagenen Programm der Schwerpunkt - wo immer es möglich ist - auf der direkten Analyse des menschlichen Systems. Allerdings wird der Einsatz von experimentellen Arten überall dort beibehalten, wo keine zuverlässige Alternative gegeben ist.

- Beurteilung und Analyse von genetischen Schäden in Eukaryoten

Spontan auftretende Genmutationen und Chromosomenaberrationen treffen den Menschen empfindlich, denn sie sind für einen wesentlichen Teil spontaner Fehlgeburten und bei Überlebenden Neugeborenen für angeborene Missbildungen sowie für geistige und körperliche Störungen verantwortlich. Nach UNSCEAR beträgt die Häufigkeit natürlich auftretender Erbmängel und Erbkrankheiten in der menschlichen Bevölkerung etwa 1% bei dominanten und X-Chromosom gebundenen Krankheiten, 0,1% bei rezessiven Krankheiten, 0,4% bei Chromosomendefekten und 9% bei angeborenen Missbildungen, die von vielen Faktoren beeinflussbar und unter unregelmässig vererbten Bedingungen entstanden sind. In Anbetracht der bekannten Tatsache, dass Strahlenwirkungen Mutationen und Chromosomenanomalien hervorrufen können, ist es daher besonders wichtig, die vorhandenen Methoden zum Nachweis von genetischen Strahlenwirkungen so weit wie möglich zu verbessern und nach Analyse der Induktionsmechanismen eine zusammenfassende Liste der verschiedenen Faktoren und Umstände zu erstellen, die für ein Ansteigen der Häufigkeitsraten eine Rolle spielen könnten.

Da das menschliche System detaillierten genetischen Analysen gewöhnlich nicht zugänglich ist, wird ein wesentlicher Teil der Forschung an anderem eukaryotischem Material durchzuführen sein. Aus der Ähnlichkeit in der Organisation der Chromosomen (DNS, Histone, usw.) und der Zellorganellen ergibt sich, dass viele Induktionsmechanismen der Kern- und Zytoplasmaschäden mit denen in menschlichen Zellen übereinstimmen. Das Programm umfasst folgende Punkte:

- a) Verbesserung und Entwicklung von Messsystemen und Versuchsmethoden zum Nachweis induzierter Veränderungen in menschlichen somatischen und Keimzellen;
- b) Klärung der Mechanismen, die zur "non-disjunction" der Chromosomen und anderen Alternationen führen, Untersuchungen zur Beziehung zwischen Chromosomenstruktur und -verhalten (Heterochromatin, Synaptonemal-Komplex und Satellit-Assoziation);
- c) Untersuchung möglicher Zusammenhänge zwischen Strahlenempfindlichkeit, Reparation und Segregationsanomalien;

- d) spezifische Untersuchungen über Wechselwirkungen und Beziehungen zwischen den biologischen Wirkungen der Strahlungen und anderer Umweltagentien;
- e) einige ausgewählte Untersuchungen zur Klärung der Strahlenwirkung auf das Genom der Mitochondrien und seine Bedeutung für das Überleben der Zelle.

- Dosis/Wirkung-Beziehung

Es ist ausserordentlich schwierig, beim Menschen die Beziehung zwischen Dosis und Wirkung zu erfassen, da nicht genügend Daten zur Verfügung stehen und da die quantitative Extrapolation von Versuchsergebnissen auf die beim Menschen vorliegenden Verhältnisse ernste Probleme stellt. In Anbetracht der Bedeutung der Dosis/Wirkung-Beziehung für die Beurteilung des Strahlenrisikos umfasst das Programm folgende Themenbereiche:

- a) Epidemiologische Erhebungen über die Beziehungen zwischen aufgenommener Dosis, Häufigkeit der Fehlentwicklungen von Lymphozyten und von biologischen Spätfolgen der Exposition (Aplasie der Keimzellen und induzierte Wirkungen bei lebend- und totgeborenen Kindern);
- b) Bestimmung der in-vivo Kinetik von Lymphozyten, um die Dosen bei nicht gleichmässiger Exposition leichter auswerten zu können;
- c) Untersuchungen mit Versuchssäugetieren (wenn möglich einschliesslich Primaten), um mehr genetische und zytogenetische Daten zu sammeln, die für die quantitative Extrapolation genetischer Strahlenschäden auf den Menschen von Nutzen sein können;
- d) Studien zur Bewertung der Methoden und Ausgangshypothesen, die bei einer Risikoabschätzung durch Extrapolation von somatischen auf Keimzellen und von Versuchsarten auf den Menschen eingesetzt werden;
- e) Untersuchungen über die Induzierung von Mutationen in Keim- und somatischen Zellen bei sehr niedrigen Dosen sowie Entwicklung von Techniken zur Erleichterung dieser Untersuchungen.

- Biochemie und Genetik der Strahlenempfindlichkeit und Reparationsvorgänge

Die Forschung, die sich mit solchen menschlichen Zellen befasst, die zu Reparationsschwäche führende Mutationen aufweisen, konnte auf den inzwischen gut fortschreitenden Erkenntnissen der Reaktionsfolgen bei der Wiederherstellung der DNS in Mikroorganismen aufbauen. Sie konnte nachweisen, dass die Mechanismen der Reparatur von DNS-Schäden für die menschliche Gesundheit von grosser Bedeutung sind. Mehrere spezifische Faktoren greifen das Reparationsvermögen an. Einer ganzen Reihe von Erbkrankheiten, mit denen erhöhte Strahlenempfindlichkeit und Krebsanfälligkeit einhergehen, liegen Mängel in der DNS-Reparatur zugrunde.

Ein grosser Teil der geplanten Forschung soll an Säugetier- und insbesondere an menschlichen Systemen durchgeführt werden. Für eine weitergehende Analyse und für die Ausarbeitung komplexer biochemischer und genetischer Mechanismen wird jedoch der Einsatz von anderem als Säugetiermaterial notwendig sein.

Das Programm umfasst folgende Themen:

- a) Überprüfung der Strahlenempfindlichkeit verschiedener menschlicher Zellen (Fibroblasten, Lymphozyten usw.), die zum einen von normalen "Kontroll"-Gruppen und zum anderen von Gruppen stammen, deren Vertreter Krankheiten mit erhöhter Empfindlichkeit gegenüber mutagenen Umweltfaktoren aufweisen. Wo es möglich ist, sollen die unter Einzelpersonen auftretenden Unterschiede der Strahlenempfindlichkeit gründlich untersucht werden.
- b) Identifizierung sowie genetische und biochemische Charakterisierung verschiedener Zelltypen von Säugetieren, die unterschiedliche Empfindlichkeit und Reparationsschwäche bei DNS-Schädigung aufweisen.
- c) Enzymologische Untersuchung der Reaktionsfolgen bei der DNS-Reparatur (sie sind bisher an Mikroorganismen, deren normale Biochemie und Genetik gut bekannt sind, am gründlichsten untersucht worden) sowie Arbeiten zur biochemischen Spezifität und biologischen Bedeutung von DNS-Verletzungen in Säugetiersystemen. Dabei sollen Proteine, die spezifische Verletzungen erkennen können, als analytische Mittel eingesetzt werden. Auf diese Weise sollen die enzymatische Wiederherstellung und der Einfluss der Verletzungen auf Mutation, Rekombination und Chromosomenaberrationen verfolgt werden.

- d) Untersuchungen der Mutagenese und der Rolle der in der Säugetierzelle vorhandenen und in die Zelle induzierbaren Reparatursreaktionen. In diesem Teil des Programms werden mehrere kürzlich aus Drosophila isolierte Mutanten, die keine DNS-Reparaturen ausführen können, eingesetzt. Bei dieser Gelegenheit kann die Rolle der DNS-Reparaturreaktionen bei einer durch Strahlen induzierten genetischen Schädigung an einem eukaryotischen Modellsystem untersucht werden.
- e) Analyse der Beziehungen von DNS-Reparation und Mechanismen, die in Zusammenhang mit der Karzinogenese stehen.

6. Abschätzung des Strahlenrisikos

Im Strahlenschutz benutzte Konzepte werden in den Mitgliedstaaten in verschiedener Weise angewandt. Aus diesem Grunde muss versucht werden, allgemein gültige Methoden für eine möglichst exakte und möglichst objektive Bewertung von Strahlenfolgen für den Menschen und seine Umwelt zu entwickeln. Die dabei erzielten Ergebnisse werden auch benötigt, wenn über Fragen des Standortes und der Art der Energieversorgung entschieden werden soll. Die 1977 von ICRP empfohlenen neuen Grundsätze für die Optimierung und Limitierung im Strahlenschutz beruhen auf einem Konzept von Risiko und Schädigung und erfordern die Beurteilung realistischer Beziehungen zwischen dosimetrischen Grössen und genetischen und karzinogenen Risiken. Neue dosimetrische Grössen und Konzepte sind entwickelt worden. Darunter befinden sich die effektive Äquivalentdosis und der Äquivalentdosisindex zur Beschreibung der individuellen Exposition sowie die kollektive Dosis und die kollektive Folgedosis für die Bewertung des kollektiven gesundheitlichen Schadens. Die praktische Anwendung dieser neuen Begriffe muss getestet und ihre Beziehung zu messbaren Grössen bestimmt werden.

Dabei sind drei Problemkreise in Betracht zu ziehen:

Der erste betrifft die Bewertung individueller und kollektiver Dosen, die sich aus normaler Ableitung und unbeabsichtigtem Freiwerden radioaktiver Substanzen ergeben. Die Bewertung der Dosen muss sich auf Daten berufen, die bei Untersuchungen des Radionuklidtransportes in der Umwelt ermittelt wurden (siehe Abschnitt 4.1.2.). Sie sollte zu einer genaueren Bestimmung der Dosisverteilung innerhalb der Bevölkerung und der Grösse der kollektiven Dosis unter Berücksichtigung der natürlichen Grundstrahlung führen. Ausserdem sind Modelle erforderlich, um jede wahrscheinliche Einwirkungsmöglichkeit auf den Menschen und seine Umwelt zu untersuchen, die den gesamten nuklearen Brennstoffkreislauf miterfassen.

Was die augenblicklich befürwortete Optimierung des Strahlenschutzes anbetrifft, so müssen auch alle Risiken mitberücksichtigt werden, die sich aus menschlichen Aktivitäten ergeben, bei denen ionisierende Strahlen eingesetzt oder die Strahlungsverhältnisse beeinflusst werden, wie medizinische Anwendungen und technologisch erhöhte Radioaktivität. Das Programm wird in sukzessiven Phasen die zu untersuchenden Themen ermitteln, die Bewertung der Dosen, denen

Arbeitskräfte und Bevölkerung ausgesetzt waren, erarbeiten und die Forschung über mögliche Schutzmassnahmen und ihre Kosten umfassen.

Der zweite Problemkreis umfasst methodologische Forschung zur Bestimmung des Schadens (detriment). Sie muss die Ergebnisse auswerten, die durch die experimentellen und epidemiologischen, in den entsprechenden Abschnitten des Programms beschriebenen Untersuchungen erzielt wurden. Dabei sollten zwei Problemgruppen behandelt werden: die Probleme der Bestimmung des Detriments im Falle mittlerer oder hoher Exposition nach einem Unfall und die Probleme im Zusammenhang mit niedrigen Dosen - und dies insbesondere bei allen berufsbedingt exponierten Personen.

Der dritte Problemkreis betrifft die Beurteilung ökonomischer und sozialer Konsequenzen bei einer Bestrahlung. Dies ist ein neues Thema, das entwickelt werden sollte, damit Hinweise zur "Optimierung" der Strahlenschutzmassnahmen gegeben werden können. Diese Massnahmen sollten sich darauf stützen, Bestahlungswerte "as low as reasonably achievable (ALARA)" vorzusehen, die wiederum an die in Europa gegebenen Bedingungen angepasst sind.

BIOLOGIE - PROTECTION SANITAIRE

Programme Radioprotection

Activités de recherche proposées 1980 - 1984.

Extrait de la proposition de la Commission
au Conseil (doc. COM(79) 158 final)

(Version originale en anglais, traduction française)

La proposition de Programme Radioprotection pour 1980-1984

Activités de recherche proposées

L'objectif du programme proposé est d'améliorer, par la coopération au niveau européen, les connaissances en matière de radioprotection, en tenant compte des problèmes particuliers et des capacités qui caractérisent l'Europe.

Le programme comportera six domaines principaux ou secteurs d'activité, qui décrivent, de façon arbitraire mais pratique, sa structure générale* :

- la dosimétrie des rayonnements et son interprétation,
- le comportement et le contrôle des radionucléides dans l'environnement,
- les effets somatiques à court terme des rayonnements ionisants,
- les effets somatiques à long terme des rayonnements ionisants,
- les effets génétiques des rayonnements ionisants,
- l'évaluation des risques d'irradiation.

Les données obtenues à partir des programmes de recherches antérieurs, et de recherches menées dans d'autres parties du monde ont été prises en considération de même que l'état actuel des connaissances tel qu'il est présenté dans le rapport UNSCEAR, les besoins futurs en matière de mesures de protection pratique et de directives ont été déterminés et les sujets de recherche appropriés ont été établis.

Le programme proposé par la Commission est basé sur les besoins prévisibles dans le domaine de la radioprotection à l'intérieur de la Communauté, ainsi que sur la mise à jour et l'adaptation des travaux déjà en cours, à la lumière de l'évolution prévue des installations nucléaires et d'autres sources de rayonnements ionisants, et de leurs effets possibles sur l'homme et sur l'environnement. Il est nécessaire de stimuler la recherche sur

* Aucune répartition de ce type ne peut définir de façon appropriée la teneur scientifique complexe d'un programme équilibré de radioprotection. Il existe un chevauchement entre secteurs, et certains sujets se rattachent à tous les secteurs concernés, ou à plusieurs d'entre eux. La dosimétrie constitue par exemple un sujet de base pour tous les secteurs, les effets de synergie sont observés dans des conditions diverses et les problèmes des doses faibles ou des débits de dose faibles, ainsi que des mécanismes fondamentaux des effets observés ou le besoin d'études épidémiologiques se manifestent dans plusieurs secteurs.

différents sujets qui sont d'une importance fondamentale pour l'avenir, et des propositions en ce sens sont présentées dans les pages qui suivent.

1. La dosimétrie des rayonnements et son interprétation

Les réglementations de radioprotection ne peuvent être appliquées correctement et les recherches sur les effets des rayonnements ionisants ne peuvent être menées de façon appropriée, que s'il est possible de déterminer la dose absorbée et/ou tout autre paramètre d'exposition, et de les interpréter en termes d'effets biologiques et de risques auxquels ces effets exposent. En outre, les directives Euratom sur les normes de base exigent des opérations de mesures et d'enregistrement de certaines données d'exposition, qui devraient être effectuées de façon comparable à l'intérieur de la Communauté. Les sujets suivants exigent ainsi une étude complétant l'ensemble du Programme Radioprotection.

- Aspects physiques de l'efficacité des rayonnements (microdosimétrie)

Les effets biologiques des rayonnements ionisants dépendent des divers paramètres d'irradiation, notamment de la qualité des rayonnements, c'est-à-dire la distribution dans le temps et dans l'espace de l'absorption de l'énergie des rayonnements et le transfert aux tissus biologiques, la distribution de l'énergie aux endroits sensibles, ainsi que les effets biochimiques immédiats. Malgré les progrès considérables accomplis en ce qui concerne les données physiques nécessaires, des recherches plus approfondies sont nécessaires pour établir des relations probantes entre la forme de l'interaction des rayonnements et les courbes doses/effets pour les irradiations externes et les radionucléides incorporés. Des recherches microdosimétriques sur l'induction des tumeurs et les défauts de fonctionnement des organes devraient pouvoir permettre de résoudre des problèmes urgents de radioprotection, notamment de vérifier si les risques liés aux doses et aux débits de dose faibles pour les rayonnements de TLE élevés et faibles ont été surestimés ou sous-estimés, et de déterminer les changements éventuellement nécessaires en ce qui concerne les facteurs de qualité, avec tous les effets que de tels changements pourraient avoir sur la conception des blindages de protection et la dosimétrie personnelle.

- Dosimétrie interne

Des recherches sont nécessaires pour mettre au point d'autres méthodes quantitatives de détermination de la dose d'irradiation effective en cas d'absorption d'isotopes radioactifs, tels que le tritium et les transuraniens, et d'inhalation d'aérosols radioactifs. Il s'agit notamment de l'amélioration des modèles dosimétriques utilisés par la CIPR pour les poumons, les intestins et les os, de l'estimation de la teneur des poumons et du corps en radionucléides émetteurs alpha à l'aide d'anthroporadiomètres, et des mesures d'excrétion. Les effets de précurseurs de l'ADN marqués dans le noyau des cellules sont également particulièrement importants pour la radioprotection.

- Dosimétrie en cas d'irradiation externe

L'irradiation externe donne lieu habituellement à des distributions de doses tout à fait hétérogènes, ou à une irradiation partielle du corps, ce qui rend parfois très difficile la détermination de la dose reçue par les organes irradiés ou les tissus exposés. C'est pourquoi les méthodes physiques doivent être améliorées, afin d'établir un rapport plus précis entre d'une part les caractéristiques de champ des irradiations extérieures, telles que l'exposition, la qualité et les différences de densité des tissus, et la dose reçue par l'organe d'autre part.

- Dosimétrie personnelle et surveillance de zone

Selon les recommandations récentes de la CIPR, la révision des normes de radioprotection doit être basée sur la recherche de méthodes d'application et d'évaluation de ces recommandations. L'introduction de l'équivalent de dose effective et de l'indice d'équivalent de dose indique que les méthodes de mesure existantes doivent être adaptées et que les facteurs de conversion et les fonctions doivent être établis théoriquement et expérimentalement pour les différentes quantités, notamment en ce qui concerne le calibrage des instruments.

Les méthodes de dosimétrie personnelle diffèrent selon les pays. On procédera à une analyse de paramètres tels que l'irradiation interne et externe, la contamination, l'incorporation et l'excrétion, qui doivent être déterminés afin de procéder à des estimations de risques, à la fois pour les expositions aiguës et chroniques et pour les mesures thérapeutiques. Les méthodes de mesure seront développées et coordonnées. Des recherches sur les normes de protection contre les particules beta devront être effectuées, ainsi que des recherches de documentation sur ces questions. Les données obtenues par des programmes d'inter-comparaison et d'études sur le terrain compléteront les résultats des recherches.

- Dosimétrie des rayonnements à TLE élevé et des neutrons

Des efforts concertés sont nécessaires actuellement pour obtenir des données sur les rayonnements à TLE élevé, y compris les neutrons d'énergies déterminées, ayant une importance pratique. Bien que de nombreuses données physiques ou méthodes de mesure de neutrons aient été publiées ou élaborées au cours des dernières années, aucune méthode entièrement satisfaisante de dosimétrie des neutrons pour le personnel, ou de dosimétrie des neutrons et de dosimétrie des rayonnements à TLE élevé pour les expériences de radiobiologie, n'a encore été mise au point. Il faudra en particulier réunir et évaluer des données susceptibles d'obtenir un consensus général sur la dosimétrie des neutrons elle-même. Les intercomparaisons demandent également un effort continu dans ce domaine, étant donné que les travaux déployés jusqu'à présent ont révélé des divergences inattendues en ce qui concerne les méthodes dosimétriques et leur précision.

Un programme de développement et d'adaptation continue de toutes les méthodes dosimétriques, correspondant aux mesures prises par le passé, est rendu nécessaire par la modification des besoins en matière de radioprotection. A cet effet, une certaine souplesse d'approche sera nécessaire pour résoudre les problèmes axés sur le programme, ou pour effectuer des études exploratoires sur les besoins actuels, ou encore pour développer de nouveaux

instruments, en garantissant ainsi la souplesse et les possibilités d'innovation future.

- L'un de ces problèmes sera celui de la dosimétrie de l'environnement. Il y aura lieu de procéder à une évaluation plus réaliste de la dose d'irradiation à laquelle le public est soumis, par suite de la radioactivité naturelle et de l'augmentation de l'exposition naturelle. Cette évaluation entre en partie dans l'estimation des risques d'exposition aux sources d'irradiation créées par l'homme.
- Un autre problème d'importance croissante est l'exposition aux rayonnements d'origine médicale. Il s'agit là de la plus importante source d'irradiation créée par l'homme, à laquelle les populations soient exposées. La recherche dosimétrique aura pour but de réduire la dose non essentielle due à cette exposition, tout en maintenant la qualité du diagnostic. Elle étudiera également l'utilité de ces données pour l'étude épidémiologique des effets des rayonnements.
- Un autre problème est la possibilité d'utiliser la dosimétrie biologique pour les accidents, afin d'obtenir des informations complémentaires importantes sur la dose effective reçue. Malheureusement ces méthodes ne se sont pas avérées entièrement satisfaisantes dans certaines situations accidentelles. Des recherches devront être effectuées sur l'amélioration des méthodes dosimétriques biologiques, et sur l'influence de débits de dose variés et de distribution non uniforme de doses dans l'espace sur les indicateurs biologiques.

2. Comportement et contrôle des radionucléides dans l'environnement

Le programme de ce secteur a pour objectif l'acquisition et l'amélioration des données sur le comportement de certains radionucléides dans diverses composantes de l'environnement. Ces données sont essentielles pour l'évaluation du détriment causé par les rayonnements, en termes de dommages potentiels pour la santé, d'activités de routine et d'événements accidentels provoquant une libération de substances radioactives dans l'environnement (voir chapitre 4.1.6). Certains sujets importants, qui sont sans rapport direct avec l'énergie nucléaire, telles que les activités humaines entraînant une exposition accrue aux rayonnements naturels, seront également considérés dans ce programme.

L'évaluation du détriment repose sur l'estimation des doses individuelles et collectives reçues par la population par le truchement de modèles représentant les cheminements différents et souvent complexes des radionucléides dans l'environnement.

En outre, les données ainsi obtenues seront utiles aux responsables délivrant les autorisations de déversement de substances radioactives dans l'environnement et fixant des limites appropriées à ces déversements, et amélioreront les bases scientifiques des programmes de contrôle de l'environnement.

De nombreuses données ont été recueillies sur le comportement de plusieurs radionucléides dans divers écosystèmes, en particulier à partir d'études des retombées radioactives dues aux essais d'armes nucléaires, ainsi qu'à partir d'expériences en laboratoire. De nombreuses lacunes subsistent cependant et la validité des données disponibles doit être améliorée.

Ce programme devrait être réalisé en assurant un équilibre satisfaisant entre les expériences en laboratoire et sur le terrain ; toutefois, un besoin accru de travaux sur le terrain se fait sentir afin de confirmer la validité des coefficients de transfert obtenus lors d'expériences en laboratoire.

Des informations utiles sur la fiabilité des coefficients de transfert et sur toute source de contamination imprévue pourraient également être obtenues, grâce aux données recueillies récemment dans le cadre de plusieurs programmes de surveillance.

La priorité sera donnée aux radionucléides et aux voies de transfert dans l'environnement susceptibles de jouer un rôle important dans les programmes d'énergie nucléaire au cours des prochaines décennies, ou par suite de l'introduction éventuelle de substances radioactives dans l'environnement à partir d'autres sources. Le programme détaillé sera élaboré en tenant compte d'autres programmes de la Communauté (voir note en bas de page) s'adressant à la sécurité nucléaire et la protection de l'environnement, ce qui permettra par conséquent de maintenir les contacts nécessaires.

L'examen des données disponibles et des travaux prévus lors des différents stades du traitement du combustible nucléaire montre que les activités suivantes sont importantes dans le contexte du programme :

- extraction et broyage de l'uranium ;
- installations d'enrichissement de l'uranium ;
- retraitement du combustible irradié ;
- recyclage du plutonium et de l'uranium et fabrication de combustibles d'oxydes mixtes ;
- introduction de systèmes élaborés de réacteurs ;
- introduction éventuelle d'autres cycles de combustible ;
- déclasséement de réacteurs nucléaires ;
- gestion, y compris élimination, des déchets liquides, gazeux et solides, produits par toutes les activités mentionnées ci-dessus.

Une attention particulière sera accordée aux méthodes d'estimation du niveau de contamination, de délimitation des zones contaminées, et de réduction ou d'élimination des transferts des radionucléides dans des situations accidentelles.

Outre les transuraniens, les radionucléides qui semblent actuellement les plus importants sont le H-3, le C-14, le S-35, le Kr-85, le Tc-99, le Ru-106, l'I-129 et l'I-131, ainsi que certains produits d'activation

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- Programme sur la gestion et le stockage des déchets radioactifs,
 - Programme sur l'utilisation du plutonium
 - Programme sur l'exploration et l'extraction de l'uranium
 - Programme sur le déclasséement des centrales nucléaires
 - Programme sur la sécurité des réacteurs à eau.

(Mn-54, Co-60) et radioisotopes naturels (radium, thorium et produits dérivés). Dans ce cadre, il faudra aussi tenir compte de la toxicité chimique de certains de ces nucléides (Tc-99, I-129).

Les différents processus de transfert dans l'environnement exigeant des recherches complémentaires sont résumés ci-dessous :

- la resuspension de radionucléides à partir de la surface des océans, de sédiments et de sols européens typiques (en particulier pour le Np, le Pu, l'Am et le Cm et pour les produits de fission à longue période) ;
- la migration des radionucléides déposés en surface des sols agricoles, vers les couches plus profondes, l'eau, les plantes et les animaux (notamment pour les transuraniens, les produits de filiation du thorium et du radium et d'autres radionucléides, notamment le S-35, le Tc-99, le Ru-106 et l'I-129). La radiocontamination des animaux par incorporation des radionucléides préalablement métabolisés et suite à une exposition chronique demande une attention particulière ;
- la migration et la rétention de radionucléides dans certaines roches et certains types de sol typiques des pays de la Communauté (notamment pour les transuraniens et les produits de fission à longue période) ;
- la rétention par les sédiments des radionucléides rejetés dans le milieu aquatique et leur mobilisation ultérieure (plus particulièrement les transuraniens et les produits de fission à longue période) ;
- la distribution confinée et le comportement des radionucléides à longue période (par exemple le C-14, le Tc-99, l'I-129), en particulier en ce qui concerne leur échange entre différentes composantes de l'environnement (par exemple échanges entre les écosystèmes aquatique et terrestre) ;
- l'absorption par des espèces aquatiques de radionucléides particuliers (par exemple le Tc-99), pour lesquels des informations complémentaires sont nécessaires ;
- l'étude des effets de synergie éventuels entre radionucléides et polluants conventionnels rejetés dans l'environnement, spécialement en ce qui concerne l'absorption des radionucléides dans la chaîne alimentaire ;
- l'échange de C-14 et HT0 entre l'atmosphère et l'environnement terrestre ;
- la dispersion atmosphérique et les processus de dépôt dans les zones urbaines.

3. Effets somatiques à court terme des rayonnements ionisants.

Le dommage radiologique commence au moment de l'irradiation. Tous les effets biologiques ultérieurs dépendent essentiellement des modifications rapides intervenant pendant une période extrêmement courte suivant l'absorption d'énergie. Une connaissance détaillée de ces processus permettrait de comprendre le mécanisme des effets de l'irradiation. On sait depuis de nombreuses années que les radicaux libres et leurs produits de réaction jouent un rôle essentiel pendant la phase initiale des lésions radiologiques, mais seules des découvertes récentes ont permis de les mesurer et de les identifier dans le matériel biologique. Des progrès considérables ont été accomplis en quelques années, et la réaction des radicaux libres radio-induits avec les acides nucléiques, qui constituent la principale cible biologique des rayonnements, est à présent bien connue. Des études complémentaires et bien coordonnées dans ce domaine, nous permettraient de comprendre le mécanisme des effets primaires des rayonnements, apportant ainsi une contribution décisive à la compréhension et au contrôle éventuel des conséquences de l'irradiation de la matière vivante.

L'étude des premiers effets cellulaires et tissulaires radio-induits, d'origine interne ou externe, sera intensifiée en raison de leur importance croissante dans l'industrie, la recherche et la médecine clinique. Les lésions pouvant faire l'objet d'un traitement comprennent essentiellement les lésions radio-induites localisées et les dommages causés au système lympho-hématopoïétique. Ces études pathogéniques sont d'une importance fondamentale pour le développement de méthodes thérapeutiques.

En raison de la grande fréquence des effets aigus, subaigus ou chroniques des lésions radio-induites locales, une attention particulière sera accordée à l'étude de leur mécanisme, de leur pronostic, de leurs complications et de leur traitement. En raison de la grande variété des modalités d'irradiation, notamment de l'irradiation externe ou interne (absorption de substances radioactives par ingestion, par inhalation ou par blessure), les parties atteintes peuvent être non seulement la peau, mais également les surfaces internes, telles que celles des voies gastro-intestinales, des voies respiratoires et de nombreux autres organes. Le tissu conjonctif et vasculaire, présent pratiquement dans toutes les parties du corps, mérite des études particulières en ce qui concerne d'éventuels effets tardifs. La fréquence

élevée de l'évolution cancéreuse suivant le processus de guérison est également typique des brûlures par irradiation. En conséquence, la pathogénèse de ces lésions, des facteurs de complication ainsi que du mécanisme et de la cinétique du renouvellement des cellules seront étudiés en détail. L'étude portera également sur les modifications antigéniques et les modifications néoplastiques éventuelles des tissus atteints, le rôle des lésions sur le système immunologique et les problèmes spécifiques posés par les greffes de peau.

Les effets précoces des rayonnements sur le système hématopoïétique par irradiation totale ou partielle du corps et le traitement des lésions consécutives ont été étudiés dans le cadre de programmes antérieurs, et des progrès considérables ont été réalisés dans la compréhension et le traitement du "syndrome hématopoïétique". Cependant, l'évaluation de l'affaiblissement et du potentiel de régénération de la fonction hématopoïétique par les méthodes de diagnostic actuelles n'est pas encore satisfaisante, notamment en ce qui concerne le diagnostic des effets subis par les cellules-souches et par certaines populations de lymphocytes. L'utilisation des préparations chromosomiques et d'autres indicateurs des lésions radio-induites sera donc étudiée. En ce qui concerne la thérapeutique, plusieurs problèmes se posent encore. De nouveaux radioprotecteurs ont été récemment découverts, et pourraient faire l'objet d'une application à l'homme, après des recherches complémentaires. Les problèmes immunologiques soulèvent les plus grandes difficultés, bien que les progrès accomplis en immunologie aient considérablement amélioré les possibilités de transplantation de la moëlle chez l'homme. Ces progrès comportent les éléments suivants : l'élimination des lymphocytes de la suspension de moëlle (séparation des cellules-souches), une amélioration importante de l'identification des spécificités tissulaires et la cryopréservation des cellules-souches (banque de moëlle), ainsi que les possibilités de "manipulation" de la réponse immunitaire, qui joue un rôle essentiel pour le sort des patients traités par greffe de moëlle (une déficience immunologique constitue la complication tardive la plus grave). Cette partie du programme de recherche portera donc essentiellement sur les problèmes immunologiques tels que :

- a. l'amélioration de la compatibilité avec les anticorps récemment découverts;
- b. la séparation et la cryopréservation des cellules-souches, comportant une méthode normalisée d'évaluation de leur viabilité;

- c. le contrôle et l'augmentation de la réponse immunitaire du receveur de moëlle greffée, afin d'éviter les complications ultérieures (infection et néoplasie radio-induite éventuelle)

4. Effets somatiques à long terme des rayonnements ionisants

Les rayonnements peuvent provoquer deux types de lésions, qui peuvent apparaître longtemps après l'exposition. Dans le premier cas, qui comporte les "effets stochastiques", la fréquence d'apparition de l'effet dépend de la dose, alors que la gravité de l'effet ne dépend pas généralement de cette dose. L'induction de tumeurs malignes constitue l'exemple le plus important d'effets de ce type.

Dans le second type, comportant les "effets non-stochastiques", on n'observe normalement aucun dommage important décelable au-dessous d'une certaine dose, mais la gravité de l'effet peut varier en fonction de la dose. L'apparition de la cataracte ou d'une diminution de la fertilité, l'affaiblissement du fonctionnement des organes ou de la circulation sanguine constituent des variantes de ce type.

- Induction d'effets stochastiques

- a. Observations sur l'homme : Les tumeurs malignes radioinduites sont particulièrement importantes dans le domaine de la radioprotection. La Commission souligne en conséquence la nécessité d'une détermination de la fréquence d'apparition des différents types de tumeurs malignes au-delà de la probabilité normale dans des groupes de personnes ayant reçu (pour raisons médicales ou autres) des doses connues, et ayant été ou pouvant être suivies pendant de longues périodes, pendant plusieurs décennies dans les meilleurs cas, pendant lesquelles des lésions radioinduites ultérieures peuvent être décelées.

Une attention particulière devrait être accordée à la dosimétrie, à la durée et à l'efficacité du contrôle des patients, à la comparabilité des séries de contrôle, à l'influence du sexe, de l'âge de l'exposition, à la mortalité provoquée par les tumeurs radioinduites, au mode de variation de l'intervalle latent entre l'irradiation et la détection des tumeurs en fonction de la dose ou d'autres facteurs, à l'influence de la qualité des rayonnements (TLE), à la variation de cette influence (EBR) en fonction de la dose, et à la forme du rapport dose/effet.

Des groupes de patients soumis à des examens radiologiques diagnostiques répétés ou intensifs seront étudiés, lorsque l'on disposera

de données complètes telles que la fréquence des décès par tumeurs malignes, etc...

Des études statistiques de patients auxquels a été appliquée une radiothérapie interne ou externe à dose modérée, en particulier dans le cas de traitements d'affections non malignes, devraient permettre d'obtenir des estimations complémentaires des risques de carcinogénèse dans les organes concernés. Ces résultats ne seront significatifs que si des valeurs de contrôle peuvent être établies pour l'apparition du cancer chez les patients souffrant des mêmes affections, mais n'ayant pas reçu de traitement par irradiation. Ces études donneraient également quelques indications sur les mesures de sécurité à prendre pour ces formes de thérapeutique. Des études similaires sur les effets de la radiothérapie des tumeurs malignes, appliquée seule ou en combinaison avec la chimiothérapie, pourraient également permettre de définir les conséquences éventuelles et les formes appropriées de traitement susceptibles de réduire au minimum la fréquence de ces risques. En outre, ces études pourraient permettre de mettre en évidence une synergie éventuelle entre l'irradiation et les agents chimiques, ou une plus grande sensibilité à la carcinogénèse par irradiation de tissus particuliers dans certaines maladies.

- b. Etudes sur les animaux : afin d'élucider le mécanisme de l'induction des cancers, il sera nécessaire d'effectuer des études expérimentales fondamentales sur la nature de ce phénomène, et sur la fréquence d'induction probable de ces modifications malignes, notamment sous l'action de doses et de débits de dose faibles. Ces informations peuvent fournir une base pour la formulation de conclusions sur la fréquence probable des altérations malignes, intervenant même après les doses les plus faibles d'irradiation dans des conditions professionnelles ou autres.

Des études sur les rapports dose/effet lors d'irradiations à faible dose, des études microdosimétriques, et des comparaisons entre une irradiation à TEL élevé et faible et une protraction de la dose seront effectuées.

Les études sur les conséquences de l'incorporation de radionucléides tiendront compte des paramètres suivants : absorption (par ingestion ou inhalation), qualité du rayonnement, demi-vie biologique, distribution dans les organes, affinité pour des tissus particuliers, hétérogénéité du dépôt, métabolisme et excrétion, et conséquences positives ou éventuellement négatives des agents chélateurs.

Une attention particulière sera accordée à la variation de facteurs susceptibles d'influencer le processus de carcinogénèse. Ces facteurs comprennent l'âge, le sexe, les hormones, les virus, le système d'immunisation et les réactions des tissus locaux, comme facteurs endogènes, ainsi que certains aspects de la carcinogénèse et des effets synergiques, comme facteur exogènes.

L'identification exacte des cellules exposées à un risque et de la série initiale et intermédiaire d'événements pendant la carcinogénèse, nécessitera la mise au point de nouvelles méthodes (notamment les marqueurs biochimiques et immunologiques). Il faudrait en outre déterminer le lien existant entre les effets mutagènes et carcinogènes.

La normalisation des expériences sur les animaux, de la nomenclature des tumeurs et de la quantification des observations morphologiques seront poursuivies.

- Inductions d'effets non-stochastiques

Pour déterminer les procédures et les doses limites appropriées pour la radioprotection, il est important de connaître les types d'effets non-stochastiques qui peuvent être induits par les rayonnements chez l'homme, la gravité de ces différents effets, et le niveau de dose auquel ils peuvent être induits. Il est particulièrement important de disposer de données sur les effets qui peuvent être induits par des doses de quelques dixièmes de sievert, chaque année, poursuivies pendant plusieurs années ou plusieurs décennies.

Cette nécessité pratique s'applique particulièrement aux tissus ou organes dans lesquels le taux d'induction mortelle de cancer par unité de dose absorbée sera probablement faible, étant donné que pour des tissus tels que les os, la peau et la thyroïde, la dose limite annuelle pourra être moins facilement déterminée par l'induction éventuelle de tumeurs malignes que par celle d'altérations non-stochastiques.

Des études seront effectuées sur la dose totale accumulée pendant une période importante de la vie d'un être humain ou d'un animal, qui produirait les mêmes effets qu'une seule dose.

On devra donc obtenir des données sur ces questions, en étudiant à la fois les effets provoqués chez l'homme et les effets induits expérimentalement chez l'animal. Chez l'homme, il est important d'étudier la dose au-delà de laquelle on observe divers effets non-stochastiques, notamment lors d'un traitement par radiothérapie au cours duquel les niveaux de dose appropriés sont atteints, mais en tenant compte également, si possible, des effets de l'irradiation à TEL élevé, et des effets d'un traitement par radionucléides s'il y a lieu. L'étude de la pathogénèse de ces effets devrait permettre de mieux comprendre l'importance des mécanismes de réparation. Il est également nécessaire à ce sujet de déterminer la nature de différences éventuelles observées entre les réactions de tissus normaux et malades aux rayonnements. Dans de nombreux cas, il est probable que les doses accumulées qui provoquent l'apparition de tumeurs malignes dans les tissus provoqueront également l'apparition de modifications non malignes. Toute interaction entre les développements de ces deux types d'effet est importante, de même que l'influence des modifications non malignes sur la fréquence des cancers. L'étude de la phase initiale du développement des effets tardifs non-stochastiques pourrait également s'avérer importante pour la détermination de la probabilité de tels effets tardifs.

En relation avec les dangers d'une exposition aux rayonnements pendant la grossesse, les effets tératogènes seront étudiés, plus particulièrement des points de vue suivants : existence éventuelle d'un seuil, influence du TLE, inactivation éventuelle, réparation des cellules embryonnaires, rapport entre les dommages aux différentes cellules de l'embryon et les accidents de développement du fœtus, rapport dose/effet aux différents stades du développement embryonnaire.

Les fréquences de radioinduction des différents types de développements défectueux (le plus souvent du système nerveux) chez l'homme et surtout sur les modèles expérimentaux devraient être aussi proches que possible.

Une réduction non spécifique de la durée de vie par les rayonnements ionisants reste encore incertaine, mais le mécanisme de cette réduction devrait faire l'objet d'études si son existence était confirmée expérimentalement.

5. Effets génétiques des rayonnements ionisants

L'étude des effets des rayonnements sur le matériel génétique est importante parce que les rayonnements peuvent augmenter la fréquence des syndromes chromosomiques et des maladies héréditaires, et qu'il est nécessaire d'effectuer des analyses détaillées des réactions de la cellule irradiée aux lésions prémutagènes et précarcinogènes.

Les objectifs généraux dans ce secteur devront fournir les informations nécessaires pour :

- déterminer, en utilisant les méthodes habituelles (méthode d'estimation directe et méthode dite des doses de doublement), les dommages génétiques radio-induits chez l'homme. Il sera nécessaire, à cet effet, d'estimer les fréquences d'apparition des maladies génétiques, de déterminer les valeurs des doses de doublement et d'évaluer la fréquence d'apparition des dommages génétiques par rad.
- comprendre les facteurs qui gouvernent, modifient ou préviennent l'apparition de dommages. Les recherches antérieures permettent de donner une description génétique et biochimique de quelques processus de réparation de l'ADN dans les cellules humaines. Une stimulation des recherches sur les mécanismes en cause pourrait non seulement permettre de poursuivre les travaux en cours, mais aussi de prévoir les interactions et les effets, d'établir les rapports entre la mutagenèse et la carcinogénèse, ainsi que de prendre les mesures de prévention ou de protection contre les dommages provoqués par les rayonnements. Elle accélérerait, en outre, la mise au point de méthodes de détection des individus sensibles, et, parmi ceux-ci, des individus hétérozygotes pour certaines anomalies génétiques qui expriment une déficience du processus de réparation et un accroissement de la sensibilité aux agents mutagènes et carcinogènes.

Le programme proposé ci-dessous met l'accent, chaque fois que cela est possible, sur l'analyse directe des systèmes humaines. L'utilisation comme matériel expérimental d'autres espèces que l'homme sera cependant maintenue dans tous les cas où il n'existe aucune autre alternative.

- Evaluation et analyse des lésions génétiques dans les eucaryotes

Les mutations géniques et les aberrations chromosomiques qui se produisent chez l'homme spontanément, constituent une source de préoccupations importantes, car elles sont responsables d'un pourcentage élevé des fausses couches non provoquées, et chez les enfants nés à terme, de malformations congénitales et de désordres mentaux et physiques. UNSCEAR a calculé que les taux d'incidence des tares et maladies héréditaires naturelles chez l'homme correspondent à approximativement 1.0 % dans le cas des maladies dominantes ou liées au sexe, 0.1 % pour les maladies à caractère récessif, 0.4% pour les maladies chromosomiques et 9.0% pour les malformations congénitales et les phénomènes héréditaires multifactoriels et anormaux. Puisque les rayonnements induisent des mutations et des anomalies chromosomiques, il importe d'améliorer dans toute la mesure du possible, les méthodes actuelles de détection des effets génétiques des rayonnements et d'inventorier, grâce à une analyse des mécanismes inducteurs, les facteurs et circonstances susceptibles d'accentuer la fréquence des phénomènes.

Comme les systèmes humains ne se prêtent généralement pas à des analyses génétiques détaillées, une partie importante de l'effort de recherche sera entrepris sur d'autres eucaryotes chez qui l'organisation des chromosomes (ADN, histones...) et des organelles cellulaires et, par voie de conséquence, de nombreux mécanismes d'induction responsables des lésions du noyau et du cytoplasme, sont identiques à ceux qui se produisent chez l'homme.

Le programme comprendra :

- a) le perfectionnement et le développement de systèmes de criblage et de méthodes expérimentales présentant un plus grand pouvoir de résolution pour la détection des mutations induites dans les cellules somatiques et dans les cellules sexuelles humaines;
- b) l'analyse des mécanismes aboutissant à la non-disjonction chromosomique et à d'autres aberrations, y compris les études des relations existant entre la structure des chromosomes et le comportement (hétérochromatine, complexe synaptinémal et association entre satellites) ;

- c) l'étude des associations éventuelles entre la radio-sensibilité, la réparation et les anomalies de ségrégation;
- d) des études spécifiques sur les interactions et les relations entre les effets biologiques des rayonnements et d'autres facteurs d'environnement;
- e) l'éclaircissement, par le biais de quelques études sélectionnées, des effets des rayonnements sur le génome mitochondrial et ses implications pour la survie cellulaire.

- Relation dose-effet

Faute de données humaines suffisantes et en raison des problèmes sérieux que pose l'extrapolation quantitative à l'homme des résultats expérimentaux, il est particulièrement difficile de déterminer la relation entre la dose et son effet chez l'homme. Compte tenu de l'importance des relations dose-effet pour l'évaluation du risque associé aux irradiations, le programme comprendra :

- a) des enquêtes épidémiologiques centrées sur l'analyse de la relation entre la dose reçue, la fréquence des anomalies lymphocytaires et les conséquences biologiques à long terme de l'exposition aux rayonnements (aplasie des cellules sexuelles et effets induits chez les enfants nés vivants et les enfants morts-nés);
- b) la détermination de la cinétique in vivo des lymphocytes, pour faciliter l'interprétation des doses résultant d'exposition non uniforme ;
- c) des recherches sur d'autres mammifères que l'homme (y compris les primates, si possible) destinées à rassembler davantage de données (génétiques et cytogénétiques) qui seront utiles pour l'extrapolation quantitative à l'homme des risques génétiques des rayonnements;
- d) l'évaluation des méthodes et des hypothèses utilisées pour extrapoler les données d'évaluation du risque des cellules somatiques aux cellules germinales et des espèces expérimentales à l'homme;

- e) des études sur l'induction, par des doses et des débits de dose très faibles, de mutations dans les cellules sexuelles et dans les cellules somatiques, ainsi que le développement de techniques destinées à faciliter de telles études.

- Biochimie et génétique de la radiosensibilité et de la réparation

L'analyse détaillée, telle qu'elle continue de se poursuivre activement, des voies conduisant à la réparation de l'ADN des microorganismes a permis la mise au point de méthodes adaptées à l'étude de cellules humaines caractérisées par des mutations qui affectent certaines étapes de la réparation des dommages radio-induits. Une telle étude a démontré la grande importance, pour la santé de l'être humain, des mécanismes gouvernant la réparation de l'ADN. Différents facteurs spécifiques influent sur les capacités de réparation et un certain nombre de maladies héréditaires, associées à une augmentation de la radiosensibilité et des affections cancéreuses, sont liées à des carences de réparation de l'ADN.

Une grande partie des recherches proposées dans ce domaine sera entreprise sur mammifères, et notamment sur l'homme, mais le recours à d'autre matériel expérimental s'imposera pour l'analyse en profondeur et la modélisation des mécanismes biochimiques et génétiques complexes.

Le programme comprendra :

- a) l'étude de la radiosensibilité d'une gamme de cellules humaines (fibroblastes, lymphocytes, etc...) prélevées sur un groupe "témoin" normal, ainsi que sur des sujets porteurs de syndromes qui confèrent une sensibilité plus forte aux mutagènes de l'environnement. Si elle s'avère possible, une analyse détaillée sera entreprise sur les variations de radio-sensibilité entre les individus;
- b) l'identification et la caractérisation génétique et biochimique de différentes souches de cellules mammifères, déficientes pour la réparation de lésions de l'ADN, qui expriment des différences de sensibilité;

- c) l'enzymologie détaillée des cheminementes intervenant dans les processus de réparation de l'ADN (une telle étude, pour être entreprise dans les meilleures conditions possibles, doit être effectuée chez les microorganismes pour lesquels la biochimie et la génétique formelles sont bien établies) et des études de la spécificité biochimique et la signification biologique des lésions de l'ADN chez les mammifères. Cette recherche impliquera les recours à des protéines qui identifient des lésions spécifiques et qui seront utilisées comme sondes analytiques pour la mesure de la réparation enzymatique et de la relation entre les lésions et la mutation, la recombinaison et les aberrations chromosomiques;
- d) l'analyse de la mutagenèse et du rôle des voies de la réparation innée et induite dans des cellules de mammifères. Il sera également fait recours, dans cette partie du programme aux différents mutants à réparation déficiente qui ont été récemment isolés chez la Drosophile et qui permettent d'étudier, chez un modèle de système eucaryotique, le rôle des différentes voies de la réparation de l'ADN dans la réalisation des dommages génétiques induits par les rayonnements;
- e) l'analyse des relations entre la réparation de l'ADN et ses mécanismes connexes d'une part et la carcinogénèse d'autre part.

6. Evaluation des risques d'irradiation

Des principes acceptés en matière de radioprotection sont susceptibles d'applications diverses dans les Etats membres. Il importe dès lors d'essayer de mettre au point des méthodes communes, aussi précises et objectives que possible, pour l'évaluation des conséquences de l'irradiation pour l'homme et son environnement. Les résultats d'un tel exercice s'imposent également lorsqu'il s'agit de décider de l'implantation et du choix du type d'alimentation énergétique. Les nouveaux principes d'optimisation et de limitation en matière de radioprotection, recommandés en 1977 par la CIPR, se fondent sur une conception des risques et des dommages et nécessitent l'évaluation réaliste des relations entre les quantités dosimétriques d'une part et les risques génétiques et carcinogènes d'autre part. On a mis au point de nouvelles quantités et de nouveaux concepts dosimétriques; parmi eux l'équivalent de dose réelle et l'indice d'équivalent de dose pour la définition de l'exposition individuelle, ainsi que la dose population et la dose engagée collective, dans le cadre de l'évaluation des dommages causés à la santé publique. L'application concrète de ces nouveaux termes doit être éprouvée et il convient de déterminer leur rapport avec des quantités mesurables.

On envisagera trois groupes de problèmes.

Le premier concerne l'évaluation des doses individuelles et collectives résultant d'émissions normales et de rejets accidentels de substances radio-actives. Cette évaluation des doses doit s'appuyer sur les données obtenues par l'étude des mouvements des radionucléides dans l'environnement (cf. 4.1.2.), et devrait conduire à une meilleure détermination de la répartition des doses parmi la population et de l'ampleur de la dose collective, compte tenu du fond naturel. Des modèles s'imposent également pour toutes les voies d'accès éventuelles à l'homme et à son environnement et ces modèles doivent porter sur la totalité du cycle nucléaire.

En ce qui concerne l'optimisation de la radioprotection qui est actuellement préconisée, il importe de tenir compte également des risques provoqués par les activités humaines qui font appel aux rayonnements ionisants ou qui ont une influence sur l'irradiation,

par exemple celles qui concernent les applications médicales et la radio-activité technologiquement renforcée. Le programme comprendra des phases successives en ce qui concerne l'identification des points à étudier, l'évaluation des doses reçues par les travailleurs et par le public et l'étude des mesures de protection possible et de leur coût.

Le second problème concerne la recherche méthodologique de l'évaluation des dommages. On utilisera les données recueillies grâce à la recherche expérimentale et épidémiologique décrite dans les secteurs ad hoc du programme. Il conviendra de retenir deux groupes de problèmes. D'abord, ceux qui concernent l'évaluation du dommage causé par une irradiation moyenne et élevée, applicable en cas d'accident. Ensuite, les problèmes relatifs aux faibles doses, qui présentent un intérêt tout particulier pour toutes les personnes exposées aux radiations sur le plan professionnel.

Le troisième problème concerne l'évaluation des conséquences économiques et sociales de l'irradiation. Il s'agit d'un nouveau thème qui devrait être développé si l'on veut mettre au point des directives pour l'optimisation de la radioprotection qui soient fondées sur l'obtention des "niveaux d'irradiation les plus faibles auxquels on puisse raisonnablement prétendre (ALARA)", dans les conditions en vigueur en Europe.

BIOLOGIA - PROTEZIONE SANITARIA

Programma di Radioprotezione

Attività di ricerca proposte 1980 - 1984.

Estratto della proposta presentata dalla
Commissione al Consiglio (doc. COM(79) 158 def.)

(Versione originale inglese, traduzione italiana)

Proposta di programma radioprotezione per il periodo 1980-1984

Attività di ricerca proposte

Il programma comunitario di radioprotezione proposto tende, attraverso uno sforzo di cooperazione europea, ad ampliare le conoscenze in materia di radioprotezione tenendo conto dei problemi particolari e delle capacità esistenti in Europa.

Il programma si compone di sei attività o settori principali importanti che in modo arbitrario ma opportuno ne indicano la struttura generale⁺:

- dosimetria delle radiazioni e sua interpretazione,
- comportamento e controllo dei radionuclidi nell'ambiente,
- effetti somatici a breve termine delle radiazioni ionizzanti,
- effetti somatici a lungo termine delle radiazioni ionizzanti,
- effetti genetici delle radiazioni ionizzanti,
- valutazione dei rischi da radiazioni.

Si è proceduto all'esame delle informazioni ricavate dai precedenti programmi di ricerca della Commissione e dalle ricerche svolte in altre parti del mondo in settori analoghi, si è passato in rassegna lo stato attuale delle conoscenze, soprattutto come risulta dalla relazione dell'UNSCEAR, sono state delineate le future esigenze in materia di misure pratiche di protezione e gli orientamenti di linee da seguire e sono stati individuati gli argomenti di ricerca necessari.

Il programma proposto dalla Commissione è fondato sulle prevedibili esigenze di radioprotezione della Comunità e sull'aggiornamento e l'adattamento delle attività già iniziate, tenendo conto dello sviluppo previsto degli impianti nucleari e di altre fonti di radiazioni ionizzanti e delle loro eventuali conseguenze sull'uomo e sull'ambiente. E' necessario stimolare la ricerca in vari settori d'importanza capitale per il futuro e a questo scopo verranno abbozzate delle proposte nella parte che segue.

⁺ Questa suddivisione non può rispecchiare in modo adeguato la complessità del contenuto scientifico d'un programma equilibrato di radioprotezione. Vi è un'apparente sovrapposizione tra i settori e vi sono argomenti collegati a tutti o a numerosi settori. Per esempio, la dosimetria è basilare in ogni settore, gli effetti sinergistici si possono osservare in vari casi e i problemi di dosi scarse e di bassi tassi di dosi come pure il meccanismo fondamentale degli effetti osservati o la necessità di studi epidemiologici si manifestano in vari settori.

1. Dosimetria delle radiazioni e sua interpretazione

L'applicazione dei regolamenti per la protezione dalle radiazioni e la ricerca sugli effetti delle radiazioni ionizzanti possono procedere in modo corretto se è possibile determinare la dose assorbita e/o altri parametri d'esposizione ed interpretarli in termini di effetti biologici e di rischi che provocano. Inoltre, le norme di base Euratom comportano la misurazione e la registrazione di alcuni dati dell'esposizione effettuate in modo comparabile in tutta la Comunità. Pertanto sono necessarie ulteriori ricerche sugli argomenti seguenti a sostegno del programma di radioprotezione nel suo insieme.

- Aspetti fisici dell'efficacia delle radiazioni (Microdosimetria)

Gli effetti biologici delle radiazioni ionizzanti dipendono da diversi parametri d'irradiazione e soprattutto dalla qualità delle radiazioni, interpretati come distribuzione spaziale e temporale dell'assorbimento d'energia delle radiazioni e di trasferimento nei tessuti biologici, (distribuzione del depositarsi dell'energia in punti sensibili oltre agli effetti biochimici immediati). Malgrado i notevoli progressi nell'acquisizione dei dati fisici necessari, servono ricerche più approfondite per stabilire una relazione convincente tra la forma d'interazione delle radiazioni e le curve dose-effetto per le radiazioni esterne e per i radio-nuclei incorporati. La ricerca microdosimetrica sull'induzione dei tumori e sulle anomalie delle funzioni organiche dovrebbe contribuire alla soluzione di gravi problemi di radioprotezione, come il fatto se i rischi relativi dovuti a dosi basse e le dosi basse o alte di radiazioni LET siano stati sopravvalutati o sottovalutati e i cambiamenti da apportare ai fattori qualitativi, con tutte le loro conseguenze sulla concezione delle schermature e sulla dosimetria personale.

- Dosimetria interna

Sono necessarie ricerche per sviluppare altri sistemi quantitativi di valutazione della dose effettiva in caso d'incorporazione di isotopi radioattivi come il tritio e gli elementi transuranici e d'inalazione di aerosoli radioattivi. Il miglioramento

dei modelli dosimetrici usati dall'ICAP per i polmoni, l'intestino e le ossa, la valutazione del contenuto di radionuclidi emettitori alfa nei polmoni e nel corpo tramite contatori per tutto il corpo e misure effettuate sugli escrementi. Gli effetti dei precursori marcati del DNA sul nucleo delle cellule sono particolarmente importanti per la protezione radiologica.

- Dosimetria in caso d'irradiazione esterna

L'irradiazione esterna provoca generalmente una distribuzione della dose poco omogenea o un'irradiazione parziale del corpo, rendendo talvolta difficile la determinazione della dose negli organi irradiati o nei tessuti in pericolo. Si devono quindi migliorare i metodi fisici per mettere meglio in rapporto le caratteristiche del campo dell'irradiazione esterna, come l'esposizione, la qualità e le differenze di densità dei tessuti, con la dose in corrispondenza dell'organo.

- Dosimetria personale e aree controllate

Secondo le raccomandazioni delle recenti pubblicazioni dell'ICAP la revisione dei livelli di radioprotezione deve essere accompagnata da ricerche sui metodi per applicare e valutare queste raccomandazioni. L'introduzione dell'equivalente della dose effettiva e dell'indice di dose equivalente comporta l'adattamento dei sistemi di misurazione esistenti e la fissazione teorica e sperimentale di funzioni e fattori di conversione per le diverse quantità, soprattutto per la taratura degli apparecchi.

Nei vari paesi esistono diversi metodi di dosimetria personale. Si analizzeranno parametri da determinare, come l'irradiazione interna ed esterna, la contaminazione, l'incorporazione e l'escrezione, per poter decidere la valutazione dei rischi per le esposizioni acute e croniche e le misure terapeutiche. I sistemi di misurazione verranno sviluppati e coordinati. Sono necessarie ricerche sui livelli di protezione da particelle beta e sulle informazioni richieste in questo campo. Le informazioni derivanti dai programmi di confronto e dagli studi sul campo completeranno i risultati delle ricerche.

- Dosimetria delle radiazioni ad alto LET e dei neutroni

E' necessario un aiuto concertato per raccogliere dati sulle radiazioni ad alto LET, compresi neutroni di energie selezionate che presentano un'importanza pratica. Sebbene negli ultimi anni siano stati pubblicati ed elaborati molti dati fisici e sistemi di misurazione per neutroni, non esistono ancora metodi pienamente soddisfacenti di dosimetria personale dei neutroni e di dosimetria delle radiazioni ad alto LET per esperimenti radiobiologici. Si dovranno raccogliere ed esaminare i dati necessari per raggiungere un accordo generale sulla dosimetria dei neutroni. In questo settore i lavori di confronto richiedono uno sforzo continuo, perchè quelli svolti finora hanno rivelato differenze inattese nelle procedure di dosimetria e nel grado di precisione.

E' necessario un programma di sviluppo continuo e d'adattamento di tutti i sistemi dosimetrici - come in passato - per far fronte alla evoluzione delle esigenze di radioprotezione. Sarà perciò necessaria una certa elasticità d'impostazione per affrontare problemi specifici, per compiere studi esplorativi sulle necessità reali o per sviluppare nuovi strumenti, ottenendo così la flessibilità e la capacità necessarie per le innovazioni future.

- Uno dei problemi sarà la dosimetria dell'ambiente. Si dovrà arrivare ad una valutazione più realistica della dose subita dal pubblico a seguito della radioattività naturale e dall'esposizione naturale ripetuta. Quest'aspetto rientra nel campo dell'accertamento del rischio da fonti di radiazione prodotte dall'uomo.

- Un'altra causa di crescente preoccupazione è l'esposizione in occasione delle diagnosi mediche, che rappresenta il maggiore contributo all'irradiazione della popolazione in generale dovuta all'uomo. La ricerca dosimetrica tenderà a ridurre la dose non essenziale di quest'esposizione, pur mantenendo la qualità d'informazione della diagnosi. Si esaminerà anche l'utilità di questi dati per gli studi epidemiologici degli effetti delle radiazioni.

- Un altro problema è la possibilità di usare la dosimetria biologica per gli incidenti in modo da ottenere importanti informazioni supplementari sulle dosi effettivamente ricevute. Purtroppo questi sistemi non si sono dimostrati completamente sufficienti in taluni casi d'incidenti. Sono necessarie ricerche per migliorare i metodi attendibili di dosimetria biologica e sull'influenza di una vasta gamma di tassi di dose e di distribuzioni spaziali non uniformi della dose sugli indicatori biologici.

2. Comportamento e controllo dei radionuclidi nell'ambiente

In questo settore il programma serve a raccogliere ed a migliorare i dati sul comportamento di determinati radionuclidi in diverse parti dell'ambiente. Tali dati sono un elemento essenziale per la valutazione del danno da radiazioni, in termini di danno potenziale alla salute, di attività abituali e di eventi (come gli incidenti) che causano emanazioni di materiale radioattivo nell'ambiente. (vedi punto 4.1.6.). Nel programma saranno inclusi argomenti importanti non legati all'energia nucleare, come le attività che espongono l'uomo con una certa intensità alle radiazioni naturali di fondo.

Per accertare il danno si devono valutare le dosi individuali e collettive delle popolazioni esposte, solitamente con l'aiuto di modelli che rappresentano come i radionuclidi vengono trasferiti lungo vari canali ambientali spesso complessi.

Inoltre questi dati saranno utili a coloro che dovranno autorizzare lo scarico di materiali radioattivi e stabilire i limiti opportuni a tale scarico nell'ambiente e miglioreranno le basi scientifiche dei programmi di controllo ambientale.

Esistono già molti dati di comportamento di numerosi radionuclidi in determinati settori dell'ambiente ricavati per esempio da studi sulle ricadute radioattive dovute ad esperimenti di armi nucleari e ad esperimenti di laboratorio. Comunque rimangono molte lacune e si deve migliorare la qualità di molti dati già disponibili.

Nell'attuazione di questo programma bisognerà mantenere un buon equilibrio tra esperimenti di laboratorio e pratici anche se è sempre più necessaria un'attività pratica per confermare la validità dei coefficienti di trasferimento ottenuti con esperimenti di laboratorio.

Informazioni utili sull'attendibilità dei coefficienti di trasferimento e su qualsiasi fonte imprevista di contaminazione potrebbero anche essere ricavate dai dati raccolti di recente in numerosi programmi di controllo.

Si darà la priorità ai radionuclidi e agli aspetti ambientali che dovrebbero diventare importanti nei programmi d'energia nucleare dei prossimi decenni o a causa dell'introduzione di materiali radioattivi nell'ambiente da altre fonti. Nel compilare il programma particolareggiato si terrà conto di altri programmi comunitari (vedi nota in calce) importanti per la sicurezza nucleare e per la protezione dell'ambiente, garantendo così opportuni contatti.

Esaminando i dati esistenti e le pratiche in vari stadi del ciclo del combustibile nucleare si osservano le seguenti attività importanti nel contesto del programma:

- estrazione e lavorazione dell'uranio
- impianti d'arricchimento dell'uranio
- ritrattamento dei combustibili irradati
- riciclaggio dell'uranio e del plutonio e fabbricazione di combustibili a ossidi misti
- introduzione di reattori avanzati
- eventuale introduzione di cicli di combustibile alternativi
- chiusura dei reattori nucleari
- gestione, compreso il deposito, dei residui liquidi, gassosi o solidi provenienti dalle attività di cui sopra.

Si dedicherà particolare attenzione ai sistemi di valutazione dei livelli di contaminazione, alla delimitazione delle aree contaminate e alla riduzione o eliminazione del trasferimento di radionuclidi in caso di incidenti.

I radionuclidi che sembrano attualmente più importanti sono gli elementi transuranici e anche H-3, C-14, S-35, Kr-85, Tc-99, Ru-106, I-129, I-131, oltre ad alcuni prodotti d'attivazione (Mn-54, Co-60) ed ai radioisotopi naturali (radio, torio e derivati). Bisognerà inoltre considerare la tossicità chimica di questi nuclidi (Tc-99, I-129).

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- Programma di gestione e deposito dei residui radioattivi
 - Programma di riciclaggio del plutonio in reattori ad acqua leggera
 - Programma d'esplorazione e d'estrazione dell'uranio
 - Programma di chiusura degli impianti nucleari
 - Programma di sicurezza dei reattori ad acqua leggera.

I più importanti processi di trasferimento nell'ambiente che hanno bisogno di ulteriori ricerche sono:

- la risospensione dei radionuclidi dalla superficie del mare, dalle melme e dai terreni tipici europei (in particolare per Np, Pu, Am, e Cm e prodotti di fissione a lungo semiperiodo);
- il trasferimento di radionuclidi depositati sulla superficie di terreni agricoli al suolo, all'acqua, alle piante ed agli animali (soprattutto per i nuclidi transuranici, delle catene di decadimento del torio e del radio ed altri radionuclidi compresi S-35, Tc-99, Ru-106, I-129). Merita particolare attenzione il modo in cui la contaminazione sistematica degli animali potrebbe essere influenzata dall'incorporazione di radionuclidi in materiali biologici e da condizioni d'esposizione cronica;
- la migrazione e la ritenzione di radionuclidi in un certo numero di rocce e di terreni caratteristici dei paesi della Comunità (in particolare per i nuclidi dei transuranici e per i prodotti di fissione a lungo semiperiodo);
- il trasferimento a sedimenti dei radionuclidi liberati nell'ambiente acquatico e la loro eventuale rimobilizzazione (in particolare per i nuclidi transuranici e per i prodotti di fissione a lungo semiperiodo);
- la distribuzione regionale ed il comportamento dei radionuclidi a lungo semiperiodo (p. es. C-14, Tc-99, I-129) con particolare riferimento al loro scambio tra vari tipi d'ambiente (p. es. scambio tra ambiente acquatico e terrestre);
- l'assorbimento di particolari radionuclidi da parte di specie acquatiche (per es. Tc-99) per il quale sono richieste maggiori informazioni;
- la ricerca di eventuali effetti sinergistici dei radionuclidi e degli inquinanti convenzionali liberati nell'ambiente con particolare attenzione per l'assorbimento dei radionuclidi nella catena alimentare;
- lo scambio di C-14 e del HTO tra l'atmosfera e l'ambiente terrestre;
- la dispersione atmosferica e i processi di deposito nelle zone urbane.

3. Effetti somatici a breve termine delle radiazioni ionizzanti

La lesione da radiazioni avviene al momento dell'esposizione. Tutti gli effetti biologici successivi dipendono essenzialmente da rapidi cambiamenti che avvengono durante un periodo di tempo estremamente breve che segue l'assorbimento d'energia. Una conoscenza approfondita di questi casi permetterebbe di capire il meccanismo degli effetti prodotti dalle radiazioni. Da molti anni si sapeva che i radicali liberi e i loro prodotti di reazione svolgono un ruolo essenziale durante la prima fase del danno radiologico, ma solo le recenti scoperte tecnologiche hanno permesso di misurarli e d'identificarli nel materiale biologico. Sono stati fatti grandi progressi in relativamente pochi anni, e attualmente la reazione fra i radicali liberi radioindotti e gli acidi nucleici, che sono il principale bersaglio biologico delle radiazioni è abbastanza ben conosciuta. Ulteriori studi in questo campo, se ben coordinati, dovrebbero portarci a comprendere chiaramente il meccanismo primario dei danni da radiazione, che sarebbe prezioso per la comprensione e l'eventuale controllo delle conseguenze dell'irradiazione sulla materia vivente.

Lo studio dei primi effetti delle lesioni da radiazioni sulle cellule e sui tessuti d'origine interna o esterna sarà approfondito tenendo conto della loro crescente importanza nell'industria e nella medicina sperimentale e clinica. Le lesioni che si possono curare comprendono soprattutto le radiolesioni localizzate e i danni al sistema linfo-emopoietico. Questi studi patogeni saranno d'importanza basilare per lo sviluppo di strategie terapeutiche.

A causa dell'alta incidenza di lesioni da radiazioni acute, subacute o croniche locali, si dedicherà un'attenzione particolare allo studio del loro meccanismo, della prognosi, delle complicazioni e della cura. A causa della grande varietà di modi d'irradiazione, sia interna che esterna, (assorbimento di materiale radioattivo per ingerimento, inalazione o ferita) esse possono avere conseguenze non solo sulla pelle, ma anche sulle superfici interne, come l'apparato digerente, l'apparato respiratorio e molti altri organi. Il tessuto connettivo e quello vascolare che

si trovano in quasi tutto il corpo richiedono studi particolari sui possibili effetti secondari. L'alta percentuale di trasformazioni cancerogene che seguono al processo di guarigione, è tipica anche per le bruciature da radiazioni. Perciò verrà studiata a fondo la patogenesi di queste lesioni, dei fattori aggravanti ed il meccanismo e la cinetica della ripopolazione cellulare. Lo studio riguarderà anche le caratteristiche dei mutamenti antigenici e le eventuali alterazioni neoplastiche del tessuto danneggiato, il ruolo della lesione al sistema immune ed i problemi specifici connessi con il trapianto della pelle.

I primi effetti delle lesioni da radiazioni sul sistema emopoietico in caso d'irradiazione totale o subtotale del corpo sono stati studiati nei programmi precedenti e sono stati compiuti notevoli progressi nella conoscenza e nel trattamento della "sindrome del midollo osseo". Peraltro l'accertamento della menomazione e del potenziale di rigenerazione delle funzioni emopoietiche con i metodi attuali non è ancora perfetto, soprattutto nella diagnosi delle lesioni di cellule primarie e di certe popolazioni di linfociti. Si studierà quindi l'uso di preparazioni cromosomiche e di altri mezzi di controllo delle lesioni da radiazioni. Per quanto riguarda la terapia, vari problemi continuano a richiamare l'attenzione. Recentemente sono stati scoperti nuovi radioprotettori che con ulteriori studi potrebbero essere validamente applicati all'uomo. I problemi immunologici continuano a presentare gravi difficoltà, anche se i progressi dell'immunologia hanno notevolmente migliorato le possibilità di trapianto del midollo nell'uomo. I progressi compiuti riguardano: la rimozione di linfociti immunologicamente reattivi dalla sospensione del midollo (separazione della cellula primaria); importanti miglioramenti nella tipizzazione dei tessuti e nella crioconservazione delle cellule (banche del midollo) e la possibilità di "manipolare" la reattività immune che svolge un ruolo centrale nell'evoluzione dei pazienti (l'insufficienza d'immunizzazione è la più grave complicazione post-incidente). Questa parte del programma di ricerca mette perciò in evidenza i seguenti problemi immunologici:

- a. miglioramento dell'accoppiamento degli antigeni dei tessuti scoperti recentemente;
- b. separazione e crioconservazione delle cellule primarie e metodo standardizzato d'accertamento della loro vitalità;
- c. controllo e aumento della reattività immune del paziente trattato al midollo per prevenire ulteriori complicazioni (infezioni ed eventuale neoplasia da radiazioni).

4. Effetti somatici ritardati delle radiazioni ionizzanti

Due tipi di effetti nocivi possono essere provocati dalle radiazioni e alcuni si possono manifestare molto tempo dopo l'esposizione iniziale. Per un tipo, che comporta il cosiddetto "effetto stocastico", la frequenza degli effetti dipende essenzialmente dall'entità della dose d'irradiazione, ma la gravità degli effetti non dipende generalmente dalla dose. L'induzione d'una malattia maligna è l'esempio più importante di questi effetti.

Per l'altro tipo, che comporta l'"effetto non stocastico", non si può scoprire normalmente nessun danno rilevante al di sotto di una certa dose, ma la gravità degli effetti prodotti può variare con la dimensione della dose. L'induzione d'una cataratta o una diminuzione della fertilità e l'indebolimento delle funzioni organiche o dell'afflusso di sangue rappresentano cambiamenti di questo tipo.

- Induzione di effetti stocastici

a. Osservazioni umane. Gli effetti maligni indotti dalle radiazioni sono particolarmente importanti in relazione alla radioprotezione e quindi la Commissione sottolinea la necessità costante d'accertare la frequenza con la quale diversi tipi di forme maligne oltrepassano le normali previsioni in gruppi di persone irradiate (per ragioni mediche o altre) con dosi note e sono o possono essere seguiti in modo esauriente per lunghi periodi, o meglio per decenni, durante i quali si potrebbero scoprire altri tumori provocati da radiazioni.

Si dovrebbe dedicare particolare attenzione alla dosimetria, alla durata e all'efficacia del controllo, alla comparabilità della serie di controlli, all'influenza del sesso e dell'età al momento dell'esposizione, alla mortalità da tumori provocati dalle radiazioni, al modo in cui l'intervallo latente tra irradiazione e scoperta dei tumori varia a seconda della dose o di altri fattori, all'influenza della qualità delle radiazioni (LET), alla variazione di questa influenza (ABE) con la dose e alla forma del rapporto dose-effetto.

Verranno esaminati gruppi di pazienti che sono stati sottoposti a indagini diagnostiche radiologiche ripetute ed estese ogni qualvolta si disporrà di dati completi come la frequenza della mortalità da forme maligne.

Studi statistici su pazienti sottoposti a radioterapia interna od esterna a dose moderata, soprattutto nel corso della terapia di malattie non maligne dovrebbero fornire ulteriori elementi sul rischio d'induzione del cancro negli organi interessati. Questi risultati saranno utili solo se si potranno stabilire dei valori di controllo per l'incidenza del cancro in pazienti colpiti dalle stesse malattie trattati con radiazioni. Questi studi dovrebbero anche fornire indicazioni sulle esigenze di sicurezza in questo tipo di terapia. Studi analoghi sugli effetti della radioterapia delle malattie maligne, da sola o combinata con la chemioterapia, potrebbero anche aiutarci a definire gli eventuali effetti secondari e le terapie adeguate per ridurre al minimo la frequenza di tali rischi. Questi studi potrebbero inoltre chiarire gli eventuali sinergismi tra le radiazioni e gli agenti chimici, o una maggiore sensibilità alla carcinogenesi da radiazioni di particolari tessuti in determinate malattie.

- b. Studi su animali. Per chiarire il meccanismo dell'induzione cancerogena servono evidentemente esperienze fondamentali sulla natura di questo fenomeno e sulla frequenza con cui rischiano di prodursi i fenomeni maligni particolarmente in relazione a dosi basse. Da queste informazioni si possono trarre valide ipotesi sulla frequenza prevedibile delle evoluzioni maligne in seguito a dosi anche più basse, legate alle esposizioni alle radiazioni per motivi professionali o d'altra natura.

Si studieranno le relazioni fra dosi ed effetti a basso dosaggio, e si svolgeranno studi microdosimetrici e di confronto delle radiazioni LET alte e basse e del prolungamento delle dosi.

Gli studi relativi agli eventi successivi all'incorporazione di radionuclidi terranno conto dei seguenti parametri: incorporazione (per ingestione o inalazione), qualità della radiazione, semiperiodo biologico, distribuzione organica, affinità per particolari tessuti, disomogeneità della sedimentazione, metabolismo ed esecuzioni e studi sui vantaggi o sui danni degli agenti chelanti.

Sarà oggetto d'attenzione anche la variazione dei fattori che possono influenzare il processo cancerogeno. Si tratta dell'età, del sesso, degli ormoni, dei virus, del sistema immunologico e delle reazioni dei tessuti locali come endogeni e di alcuni aspetti degli effetti cocancerogeni e sinergistici come fattori esogeni.

Per l'identificazione esatta delle cellule in pericolo e del processo iniziale e intermedio durante la cancerogenesi sarà necessario sviluppare nuovi metodi (compresi i marcatori biochimici ed immunologici). Inoltre, si dovrebbe chiarire il legame tra effetti mutagenetici e cancerogeni. Continuerà la standardizzazione degli esperimenti su animali, della nomenclatura dei tumori e della quantificazione degli estremi morfologici.

- Induzione di effetti non stocastici

Nel determinare le procedure e le dosi limite nella protezione dalle radiazioni è importante conoscere i tipi di effetti non stocastici che le radiazioni possono produrre nell'uomo, la gravità di questi vari effetti e la dose a cui rischiano di presentarsi. E' particolarmente importante avere informazioni sugli effetti che potrebbero essere provocati da dosi equivalenti a qualche decimo di sievert all'anno protratte per molti anni o decenni.

Questa esigenza pratica riguarda soprattutto i tessuti e gli organi per i quali il tasso d'induzione di forme di cancro mortale per unità di dose assorbita è normalmente basso, dato che per tessuti come le ossa, la pelle e la tiroide è meno probabile che la dose limite annuale sia determinata da eventuali induzioni di forme maligne che non da evoluzioni dannose non stocastiche.

Si cercheranno negli uomini e negli animali informazioni sulla dose totale accumulata per una quota ingente della vita dell'uomo o dello animale, che provocherebbe gli stessi effetti di una dose singola.

Per ottenere informazioni su questi problemi occorre esaminare sia gli effetti prodotti sull'uomo che quelli provocati sperimentalmente negli animali. Nell'uomo è importante rilevare la dose oltre la quale si osservano vari effetti non stocastici, soprattutto durante la radioterapia nella quale si raggiungono gli adeguati livelli di dose, ma includendo se possibile gli effetti delle radiazioni ad alto LET ed eventualmente quelli del trattamento con radionuclidi. Lo studio della patogenesi di questi effetti potrebbe chiarire l'importanza dei

meccanismi di recupero.

In questo contesto è anche necessario accertare la natura di eventuali differenze tra le reazioni alle radiazioni di tessuti normali e malati. In molti casi è da prevedere che le dosi accumulate, che provocano evoluzioni maligne in un tessuto avrebbero comunque causato o iniziato evoluzioni non maligne. Qualsiasi interazione tra lo sviluppo di questi due tipi di effetti o l'influenza delle evoluzioni non maligne sulla frequenza dei cancro sono importanti. L'esame della fase iniziale dello sviluppo di effetti tardivi non stocastici potrebbe anche essere importante per determinare la probabilità di tali effetti.

Quanto al rischio inerente a qualsiasi esposizione alle radiazioni durante la gravidanza, si studieranno gli effetti teratogeni, con particolare riferimento all'eventuale esistenza di una soglia, all'influenza del LET, all'eventuale inattivazione, al recupero o restauro delle cellule embrionali, ai rapporti tra i danni alle singole cellule dell'embrione e insufficienze gravi nello sviluppo del feto, alla relazione dose/effetto nelle varie fasi dello sviluppo embrionale.

Le frequenze con le quali diversi tipi di difetti di sviluppo (generalmente nel sistema nervoso) sono indotti da radiazioni nell'uomo e in ogni modello sperimentale dovrebbero essere più vicine possibile.

E' ancora incerto se le radiazioni ionizzanti determinino una riduzione non specifica della durata della vita, ma se l'esistenza di questo fenomeno venisse provata sperimentalmente occorrerebbe studiarne il meccanismo.

5. Effetti genetici delle radiazioni ionizzanti

Lo studio degli effetti delle radiazioni sul materiale genetico è importante perchè le radiazioni potrebbero aumentare l'incidenza delle sindromi dei cromosomi e delle malattie ereditarie e perchè sono necessarie analisi particolareggiate dei legami complessi attraverso i quali le cellule irradiate affrontano le lesioni pre-mutageniche e precancerogene. Quindi gli obiettivi generali in questo settore sono di ottenere le informazioni necessarie per:

- accertare con i metodi attualmente disponibili (metodo della valutazione diretta e metodo del raddoppio della dose) il danno genetico provocato nell'uomo dalle radiazioni. Occorrono fra l'altro stime sulla frequenza delle malattie genetiche alla nascita, la determinazione dei valori delle doppie dosi e una valutazione dei difetti genetici per rad;
- comprendere i fattori che regolano, modificano od impediscono il verificarsi del danno. Grazie alle ricerche svolte in passato è ora possibile caratterizzare geneticamente e biochimicamente alcuni dei processi di ricostituzione del DNA nelle cellule umane. Stimolando la ricerca per chiarire i meccanismi oltre a permettere di continuare il lavoro si possono ottenere in ultima analisi i mezzi per prevedere le interazioni e gli effetti, per determinare i rapporti tra la mutagenesi e la cancerogenesi e per prevenirsi o proteggersi dai danni da radiazioni. Si dovrebbe anche accelerare lo sviluppo dei metodi per individuare le persone sensibili e tra queste quelle che siano eterozigoti per malattie genetiche che comportano un'insufficienza del recupero e che abbiano una sensibilità aumentata agli agenti mutageni e ai cancerogeni.

Per raggiungere questi obiettivi nel programma proposto si pone l'accento, quando possibile, sull'analisi diretta dei sistemi umani. Ma l'uso di specie sperimentali viene mantenuto in tutti i casi in cui non vi sia un'alternativa accettabile.

- Accertamento e analisi delle lesioni genetiche negli eucarioti

Le mutazioni genetiche e le aberrazioni cromosomiche che si producono spontaneamente nell'uomo sono fonti di notevoli difficoltà, dato che da esse dipendono gran parte degli aborti spontanei e nei casi di gravidanze portate a termine, le malformazioni congenite e i disturbi mentali e fisici. L'incidenza delle malformazioni e malattie ereditarie naturali nella popolazione è stata calcolata dall'UNSCEAR a circa 1% per le malattie dominanti e connesse, allo 0,1% per le malattie recessive, allo 0,4% per le malattie cromosomiche e al 9% per le malformazioni congenite causate da diversi fattori ereditari. Poichè è noto che le radiazioni producono mutazioni e anomalie cromosomiche, è particolarmente importante migliorare per quanto è possibile gli attuali metodi di rilevazione degli effetti genetici delle radiazioni e definire, grazie ad un'analisi dei meccanismi d'induzione, l'elenco dei diversi fattori e circostanze che potrebbero contribuire ad un aumento del tasso d'incidenza.

Dato che i sistemi umani non si prestano generalmente ad analisi genetiche particolareggiate, gran parte delle ricerche verrà svolta su altro materiale eucariotico, dove data la similitudine dell'organizzazione cromosomica (ADN, istoni ...) e di organelli cellulari, molti meccanismi d'induzione dei danni al nucleo ed al citoplasma sono identici a quelli dell'uomo. Il programma comprende:

- a) il miglioramento e lo sviluppo di sistemi d'analisi e di metodi sperimentali con maggiore potere risolvante per individuare le alterazioni indotte nelle cellule somatiche e negli embrioni dell'uomo,
- b) la spiegazione del meccanismo che porta alla non disgiunzione cromosomica e ad altre aberrazioni, compresi gli studi delle relazioni tra struttura cromosomica e comportamento (eterocromatina, complesso sinattinemale e associazioni satelliti),
- c) studio delle eventuali associazioni tra radiosensibilità, restauri e anomalie segregazionali,

- d) studi specifici sulle interazioni e relazioni tra gli effetti biologici delle radiazioni e altri agenti ambientali,
- e) spiegazione, attraverso pochi studi scelti, degli effetti dell'irradiazione sul genoma mitocondriaco e sulle sue applicazioni per la sopravvivenza cellulare.

- Rapporto fra dose ed effetto

E' particolarmente difficile stabilire il rapporto tra dose ed effetto nell'uomo, perchè non vi sono dati umani sufficienti e perchè l'estrapolazione quantitativa dei risultati sperimentali all'uomo pone seri problemi. Tenendo conto dell'importanza del rapporto dose-effetto per l'accertamento dei rischi da radiazione, il programma comprende:

- a) studi epidemiologici che pongono l'accento sul rapporto tra la dose ricevuta, le frequenze delle aberrazioni dei linfociti e le conseguenze biologiche a lunga scadenza dell'esposizione (aplasia nelle cellule germinali ed effetti indotti nei bambini nati vivi ed in quelli nati morti),
- b) determinazione della cinetica in vivo dei linfociti per facilitare l'interpretazione di dosi da esposizione non uniformi,
- c) ricerche su specie sperimentali di mammiferi (compresi i primati, se possibile) per raccogliere maggiori dati (genetici e citogenetici) che saranno utili per estrapolazioni quantitative dei rischi genetici da radiazioni per l'uomo,
- d) studi di valutazione dei metodi e ipotesi relative all'accertamento dei rischi nella estrapolazione da cellule somatiche a cellule germinali e da specie sperimentali all'uomo,
- e) studi sull'induzione di mutazioni in cellule germinali e somatiche a dosi molto basse e sviluppo di tecniche per facilitare questi studi.

- Biochimica e genetica della radiosensibilità e restauro

Grazie alla conoscenza ormai molto avanzata dei processi di restauro del DNA nei microrganismi, le ricerche in cui vengono impiegate cellule umane le cui mutazioni tendono a colmare i difetti, hanno dimostrato che i meccanismi di restauro dei danni al DNA sono di grande importanza per la salute umana. Diversi fattori specifici influenzano le possibilità di recupero e varie malattie ereditarie che sono accompagnate da un aumento della sensibilità alle radiazioni e dell'incidenza del cancro dipendono da difetti di restauro del DNA.

Una gran parte della ricerca prevista verrà fatta sui sistemi di mammiferi e in particolare su quelli umani, ma sarà necessario usare materiale non mammifero per l'analisi in profondità e per costruire modelli dei complessi meccanismi biochimici e genetici.

Il programma comprenderà:

- a) l'esame della radiosensibilità di varie cellule umane (fibroblasti, linfociti, ecc.) prelevate da un normale gruppo di "controllo" e da rappresentanti di quelle malattie umane che mostrano un aumento di sensibilità agli agenti mutageni ambientali. Quando possibile, si procederà ad un'analisi particolareggiata delle variazioni nella radiosensibilità fra singoli individui,
- b) l'identificazione e la caratterizzazione genetica e biochimica di catene di cellule di mammiferi a costituzione variabile e con diversa sensibilità e insufficienti a restaurare i danni del DNA,
- c) la ricerca dettagliata dell'enzimologia dei processi di restauro del DNA (quest'aspetto viene attualmente studiato con successo nei microrganismi dove la biochimica formale e la genetica sono avanzate) e studi delle particolarità biochimiche e del significato biologico delle lesioni del DNA nei sistemi di mammiferi. La ricerca comprenderà l'uso, come sonde analitiche, di proteine che individuano lesioni specifiche per controllare il restauro enzimatico e la relazione fra lesioni, mutazioni, ricombinazioni e aberrazioni cromosomiche,

- d) gli studi della mutagenesi e il ruolo delle capacità di restauro costitutive e inducibili nelle cellule di mammiferi. In questa parte del programma si utilizzeranno anche vari agenti mutanti con insufficiente capacità di restauro del DNA, recentemente isolati nella Drosophila, che permettono di studiare il ruolo dei processi di restauro del DNA per ottenere lesioni genetiche provocate da radiazioni in un sistema a modello eucariotico,
- e) l'analisi delle relazioni tra il restauro del DNA e i relativi meccanismi che portano alla cancerogenesi.

6. Valutazione dei rischi da radiazioni

I concetti usati nella protezione dalle radiazioni possono essere applicati in modo diverso nei vari Stati membri. Per questo motivo è necessario cercare di definire metodi comuni per accertare nel modo più accurato e più obiettivo possibile le conseguenze delle irradiazioni per l'uomo e per il suo ambiente. I risultati di questo esercizio sono anche necessari per prendere decisioni relative all'ubicazione degli impianti e all'approvvigionamento d'energia. I nuovi principi d'ottimizzazione e di limitazione della protezione dalle radiazioni, che sono stati suggeriti nel 1977 dallo ICRP, si basano sul concetto di rischio e di danno e richiedono l'accertamento di relazioni realistiche tra quantità dosimetriche e rischi genetici e cancerogeni. Sono stati sviluppati nuovi concetti e quantità dosimetrici tra cui l'equivalente della dose e l'indice equivalente della dose per la descrizione delle singole esposizioni e la dose collettiva e l'impegno di dose collettiva per l'accertamento dei danni alla salute pubblica. E' necessario sperimentare l'applicazione pratica di questi nuovi termini e bisogna determinarne il rapporto con le quantità misurabili.

Si devono considerare tre gruppi di problemi.

Il primo è l'accertamento delle dosi individuali e collettive dovute all'emissione normale e accidentale di sostanze radioattive. La valutazione delle dosi deve basarsi sui dati ottenuti dallo studio dei movimenti di radionuclidi nell'ambiente come descritto nel punto 4.1.2., e dovrebbe portare ad una migliore definizione della distribuzione delle dosi tra la popolazione e dell'ordine di grandezza della dose collettiva, tenendo conto della radiazione naturale di fondo. Sono necessari modelli anche per ogni possibile via d'accesso all'uomo e al suo ambiente per l'intero ciclo del combustibile nucleare.

Per quanto riguarda l'ottimizzazione della radioprotezione di cui si parla correntemente, si deve tener conto anche di tutti i rischi derivanti dalle attività umane che comportano l'uso di radiazioni ionizzanti o che influenzano l'irradiazione, come le applicazioni mediche e l'aumento della radioattività dovuto alla tecnologia. Il programma comprenderà più fasi successive per

identificare i punti da studiare, per accertare le dosi assorbite dai lavoratori e dal pubblico e per cercare eventuali misure di protezione, valutandone il costo.

Il secondo problema è la ricerca metodologica sull'accertamento del danno per la quale si deve far uso dei dati ottenuti attraverso le ricerche sperimentali ed epidemiologiche descritte nel relativo capitolo del programma. Dovrebbero essere considerati due tipi di problemi. Innanzitutto quelli dell'accertamento del danno da irradiazioni a medio ed alto livello, che si verificano in caso d'incidente. Quindi quello relativo a basse dosi che interessa particolarmente tutte le persone esposte per motivi professionali.

Il terzo problema è l'accertamento delle conseguenze economiche e sociali dell'irradiazione. Questo è un argomento nuovo che dovrebbe essere sviluppato in modo da stabilire gli orientamenti per l'"ottimizzazione" delle attività di radioprotezione, sulla base dei "livelli più bassi possibili" ("ALARA": as low as reasonably achievable) nelle condizioni esistenti in Europa.

BIOLOGIE - BESCHERMING VAN DE GEZONDHEID

Programma Stralingsbescherming

Voorgestelde onderzoek activiteiten 1980 - 1984.

Uittreksel van het voorstel van de Commissie aan
de Raad (doc. COM(79)158 def.)

(Originele versie in het engels, nederlandse vertaling)

Voorstel voor het Programma Stralingsbescherming 1980-1984

Voorgestelde onderzoekactiviteiten

Het voorgestelde Programma voor Stralingsbescherming van de Gemeenschap heeft ten doel door middel van Europese samenwerking te komen tot een uitbreiding van de kennis op het gebied van de stralingsbescherming, met inachtneming van de bijzondere problemen en deskundigheden die in Europa aanwezig zijn.

Het programma zal bestaan uit zes hoofdactiviteiten of sectoren die een

- willekeurige maar handige - indeling van de totale opzet vormen*:

- stralingsdosimetrie en de interpretatie hiervan,
- gedrag van en controle op radionucliden in het milieu
- somatische effecten op korte termijn van ioniserende stralingen,
- somatische effecten op lange termijn van ioniserende stralingen,
- genetische effecten van ioniserende straling
- beoordeling van stralingsrisico's.

De informatie, die is ontleend aan voorafgaande onderzoekprogramma's van de Commissie en aan elders in de wereld verrichte onderzoekingen werd bestudeerd, de huidige stand van de kennis werd herzien, met name zoals deze is weergegeven in het rapport van de UNSCEAR, de toekomstige behoeften aan praktische beschermingsmaatregelen en richtlijnen werden omschreven en de gebieden waarop onderzoek dient te worden verricht werden vastgesteld.

Het door de Commissie voorgestelde programma is gebaseerd op de te verwachten behoeften aan stralingsbescherming in de Gemeenschap en op de samenwerking en aanpassing van de activiteiten die reeds aan de gang zijn, in het licht van de verwachte ontwikkeling van nucleaire installaties en andere bronnen van ioniserende straling en de mogelijke effecten hiervan op mens en milieu. Het is noodzakelijk het onderzoek inzake de verschillende onderwerpen, die van cruciale betekenis zijn voor de toekomst, te stimuleren en voorstellen dienaangaande zijn uitgewerkt op de volgende bladzijden.

* Geen enkele onderverdeling kan op adequate wijze de ingewikkelde wetenschappelijke inhoud van een evenwichtig programma voor stralingsbescherming afbakenen. Er is een duidelijke overlapping van sectoren en er zijn onderwerpen die tot alle of tot verscheidene sectoren behoren.

Dosimetrie bijvoorbeeld is een fundamenteel vereiste voor alle sectoren, synergetische effecten worden onder vele verschillende omstandigheden waargenomen en de problemen van lage doses of lage dosistempo's alsmede de fundamentele werking van de waargenomen effecten of de noodzaak van epidemiologische studies doen zich voor in verscheidene sectoren.

1. Stralingsdosimetrie en de interpretatie hiervan

De toepassing van voorschriften voor stralingsbescherming en onderzoek inzake de gevolgen van ioniserende straling kunnen alleen op de juiste wijze plaatsvinden als het mogelijk is de geabsorbeerde dosis en/ of andere bestralingsparameters te bepalen en deze te interpreteren in termen van biologische effecten en het risico waartoe zij aanleiding geven. Voorts vereisen de richtlijnen van Euratom inzake de Basisnormen het meten en registreren van bepaalde bestralingsgegevens die binnen de Gemeenschap op een vergelijkbare wijze dienen te worden uitgewerkt. De volgende onderwerpen dienen derhalve verder te worden bestudeerd ter ondersteuning van het Programma Stralingsbescherming in zijn geheel.

- Fysische aspecten van stralingseffecten (microdosimetrie)

De biologische effecten van ioniserende straling zijn afhankelijk van verschillende bestralingsparameters, met name van de stralingskwaliteit, geïnterpreteerd als de ruimtelijke en tijdelijke verdeling van de absorptie van stralingsenergie en de overdracht daarvan in biologische weefsels de verdeling van energie-afzetting binnen gevoelige plaatsen alsmede de onmiddellijke biothermische effecten. Ondanks de aanzienlijke vooruitgang die geboekt werd bij het verzamelen van de vereiste fysische gegevens, zijn verdere onderzoeken nodig om de overtuigende relaties tussen de vorm van stralingsinteractie en de dosis-effect curves voor uitwendige bestraling en opgenomen radionucliden vast te stellen.

Microdosimetrisch onderzoek inzake het tumorinductie en stoornissen van orgaanfuncties moeten een bijdrage kunnen leveren tot de oplossing van dergelijke brandende vraagstukken op het gebied van de stralingsbescherming, zoals de vraag of de relatieve risico's van lage doses en dosistempo's van zowel lage als hoge LET-stralingen werden overschat of onderschat, en of zij enige wijziging nodig hebben gemaakt van de kwaliteitsfactoren, met alle gevolgen die dergelijke wijzigingen zouden kunnen hebben voor het afschermingsplan en de persoonlijke dosimetrie.

- Interne dosimetrie

Er is onderzoek nodig om verdere kwantitatieve methoden te ontwikkelen voor de vaststelling van de effectieve stralingsdosis in geval van opname van radioactieve isotopen zoals tritium en de transuranen en de inademing van radioactieve aerosolen. De verbetering van dosimetrische modellen die door de ICRP gebruikt worden voor longen, darmen en botten, schatting van het gehalte in lichaam en longen aan alpha-emitterende radionucliden door respectievelijk een "whole body counter" en excretiemetingen. De effecten van gemerkte DNA - precusoren in de celkern zijn eveneens van speciale betekenis voor de stralingsbescherming.

- Dosimetrie in geval van externe bestraling

Externe bestraling geeft gewoonlijk aanleiding tot heel inhomogene dosisverdelingen of tot een gedeeltelijke lichaamsbestraling, waardoor het soms moeilijk wordt de dosis in bestraalde organen of weefsels die bedreigd worden vast te stellen. De fysische methoden zijn derhalve verbeterd, teneinde de karakteristieken van externe bestraling, zoals blootstelling en kwaliteit en verschillen in weefsel-dichtheid wat exacter in relatie te brengen tot de orgaan-dosis.

- Persoonlijke dosimetrie en zonebewaking

N.a.v. de aanbeveling in recente publicaties van de ICRP dient herziening van de normen op het gebied van de stralingsbescherming te worden geruggesteund door onderzoek betr. methoden die ten doel hebben deze aanbevelingen toe te passen en te evalueren. De invoering van de effectie dosis-equivalent en dosisequivalent-index betekent dat bestaande methoden moeten worden aangepast en conversiefactoren en -functies theoretisch en proefondervindelijk moeten worden vastgesteld voor de verschillende hoeveelheden, met name wat betreft het ijken van instrumenten.

Er zijn verschillende manieren om de persoonlijke dosimetrie in de diverse landen uit te werken. Er zal een analyse worden gemaakt van parameters, zoals interne en externe bestraling, besmetting, incor-

poratie en afscheiding, die moeten worden bepaald, teneinde beslissingen te nemen inzake risico-schattingen zowel voor acute als voor chronische bestralingen en therapeutische maatregelen. Er zullen meetmethoden worden ontwikkeld en gecoördineerd. Er is onderzoek vereist inzake beschermingsnormen voor bèta-deeltjes en inzake de informatie die nodig is voor dit doel. Informatie ontleend aan onderlinge vergelijkbare programma's en veldstudies zullen de onderzoek-resultaten aanvullen.

- Dosimetrie van high-IET- straling en neutronen

Gezamenlijke inspanning is momenteel noodzakelijk om gegevens te verzamelen betr. high-IET-stralingen met inbegrip van neutronen met geselecteerde energien van praktische betekenis.

Hoewel in de afgelopen jaren vele fysische gegevens en meetmethoden voor neutronen zijn gepubliceerd of uitgewerkt, moeten volledig bevredigende methoden inzake persoonlijke neutronendosimetrie alsmede voor neutronen- en high-IET-dosimetrie voor radiobiologische proeven nog worden ontwikkeld. Een van de problemen daarbij zal ongetwijfeld zijn het verzamelen en evalueren van gegevens die een algemene consensus mogelijk maken, die m.b.t. de neutronendosimetrie zelf moet worden bereikt.

Op dit gebied dient ook voortdurend aandacht te worden besteed aan onderlinge vergelijkingen, aangezien die welke werden uitgewerkt onverwachte discrepanties m.b.t. de dosimetrie-procedures en de nauwkeurigheid hiervan aan het licht brachten.

Een programma van voortdurende ontwikkeling en aanpassing voor alle dosimetrische methoden - zoals in het verleden heeft plaatsgevonden - is vereist om het hoofd te bieden aan de veranderende behoeften op het gebied van stralingsbescherming. Daarvoor is een flexibele benadering vereist, teneinde taakgerichte problemen aan te pakken of oriënterende studies uit te werken van de huidige behoeften of om nieuwe instrumenten te ontwikkelen, en daarmee de flexibiliteit en de mogelijkheden voor vernieuwing in de toekomst te garanderen.

- Een van deze problemen zal zijn de omgevingsdosimetrie. Er dient een meer realistische schatting te worden gemaakt van de dosis voor het publiek die het resultaat is van natuurlijke radioactiviteit en daaruit voortvloeiende natuurlijke bestraling. Dit vormt een onderdeel van de eigenlijke beoordeling van het risico van niet-natuurlijke stralingsbronnen.
- Een ander probleem dat aanleiding geeft tot toenemende zorg is de bestraling t.b.v. medische diagnose. Dit vormt de grootste bijdrag van niet-natuurlijke bestralingsbronnen voor de bevolking in het algemeen. Dosimetrisch onderzoek zal erop gericht zijn de niet-essentiële dosis van deze bestraling te beperken, met handhaving van de kwaliteit van de diagnostische informatie. Het onderzoek zal ook het nut van dergelijke gegevens voor epidemiologische studies van stralingseffecten bestuderen.
- Een derde probleem is de mogelijkheid van het gebruik van biologische dosimetrie voor ongevallen, teneinde belangrijke aanvullende informatie te verstrekken betreffende de ontvangen effectieve dosis. Helaas bleken deze methoden in bepaalde ongevalsituaties niet helemaal bevredigend te zijn. Onderzoek is dan ook noodzakelijk m.b.t. de verbetering van betrouwbare biologische dosimetrische methoden en de invloed van een uitgebreid gamma van dosistempo's en niet-uniforme ruimtelijke dosis-verdelingen over de biologische indicatoren.

2. Gedrag van en controle op radionucliden in het milieu

Het programma van deze sector is gericht op het verzamelen en uitwerken van gegevens omtrent het gedrag van bijzondere radionucliden in verschillende componenten van het leefmilieu. Dergelijke gegevens vormen een wezenlijke bijdrage tot de vaststelling van stralingsletsel, in termen van potentiële schade voor de gezondheid, van routine-werkzaamheden en gebeurtenissen (zoals ongevallen) die leiden tot het vrijkomen van radioactieve stoffen in de omgeving (zie paragraaf 4.1.6.). Belangrijke onderwerpen, die geen verband houden met kernenergie, maar wel in het programma zullen worden opgenomen, zijn die menselijke activiteiten als gevolg waarvan mensen in toenemende mate worden blootgesteld aan natuurlijke achtergrondstraling.

De vaststelling van de stralingsschade vereist de schatting van individuele en collectieve doses bij de aan straling blootgestelde bevolking, gewoonlijk door middel van modellen die weergeven op welke wijze radionucliden langs verschillende en veelal ingewikkelde wegen in het milieu worden overgebracht.

Daarnaast zullen deze gegevens een hulpmiddel betekenen voor diegenen, die verantwoordelijk zijn voor het verlenen van toestemming voor de lozing van radioactieve stoffen en die doeltreffende grenzen moeten stellen aan dergelijke lozingen in het milieu terwijl zij tevens de wetenschappelijke basis voor programma's inzake milieubeheer zullen verbeteren.

Vele gegevens werden reeds bijeengebracht over het gedrag van verscheidene radionucliden in speciale sectoren van het milieu, bijvoorbeeld als het resultaat van fallout-studies i.v.m. de beproeving van kernwapens in de atmosfeer en i.v.m. laboratoriumproeven. Er blijven echter nog vele lacunes, en veel van de beschikbare gegevens dient kwalitatief te worden verbeterd.

Bij de tenuitvoerlegging van dit programma zal een redelijk evenwicht tussen laboratoriumproeven en veld-experimenten noodzakelijk zijn; hoewel er een toenemende behoefte bestaat aan veldwerk, teneinde de geldigheid van overdracht-coëfficiënten, afgeleid van laboratoriumproeven, te bevestigen.

Nuttige informatie betr. de betrouwbaarheid van de overdrachts-coëfficiënten en alle onverwachte bronnen van besmetting kunnen ook worden afgeleid van gegevens die onlangs in het kader van verschillende stralingscontrole programma's werden verzameld.

Er zal prioriteit worden gegeven aan die radionucliden en milieu-wegen die de komende decennis wel eens belangrijk zouden kunnen worden in het kader van kernenergie-programma's of als gevolg van radioactieve stoffen die, afkomstig van andere bronnen, in het milieu kunnen worden gebracht. Bij de compilatie van het gedetailleerde programma zal rekening worden gehouden met andere communicatieve programma's (zie voetnoot), die deel uitmaken van de nucleaire veiligheid en de bescherming van het milieu, waardoor de garantie wordt gegeven dat deze op doeltreffende wijze op elkaar zullen worden afgestemd. Herzieningen van bestaande gegevens en verwachte werkwijzes in verschillende stadia van de splijtstofkringloop wijzen erop dat de volgende activiteiten in het kader van het programma belangrijk zijn :

- uraniummijnen en uraniumerts verwerking
- uraniumverrijkingsinstallaties
- opwerking van bestraalde splijtstoffen
- terugvoer van uranium en plutonium en de vervaardiging van gemengde oxydesplijtstoffen
- de invoering van geavanceerde reactorsystemen
- de mogelijke invoer van alternatieve splijtstofkringlopen
- ontmanteling van kernreactoren
- het beheer, inclusief de lozing van vloeibare, gasvormige en vaste afvalstoffen, die door alle bovengenoemde activiteiten kunnen ontstaan.

Er zla bijzondere aandacht worden besteed aan methoden voor het schatten van besmettingsniveaus, afbakening van besmette gebieden en beperking of uitschakeling van de overdracht van radionucliden in geval van een ongeval.

- Programma betr. beheer en opslag van radioactieve afvalstoffen
- Programma betr. de terugvoer van plutonium in licht-waterreactoren
- Programma betr. de exploratie en extractie van uranium
- Programma betr. de ontmanteling van kernenergiecentrales
- Programma betr. de veiligheid van licht-waterreactoren.

Radionucliden die momenteel het belangrijkst schijnen zijn de transuranen tevens H-3, C-14, S-35, Kr-85, Tc-99, Ru-106, I-129, I-131 alsmede bepaalde activeringsprodukten (Mn-54, CO-60) en natuurlijk radioisotopen (radium, thorium en dochterprodukten). De chemische toxiciteit van sommige van deze nucliden (Tc-99, I-129) moet ook in aanmerking worden genomen.

De voornaamste overdrachtsprocessen in het milieu waarvoor verder onderzoek noodzakelijk is, zijn heironder beknopt weergegeven :

- hersuspensie van radionucliden uit het oppervlak van de zee, slib en typische Europese land-oppervlakken (met name voor Np, Pu, Am en Cm en lang levende splijtingsprodukten);
- de overdracht van radionucliden afgezet op het oppervlak van landbouwgrond op bodem, water, flora en fauna (met name voor de transurannucliden, leden van de thorium en radium verval-ketens en andere radionucliden, met inbegrip van S-35, Tc-99, Ru-106, I-129).

De wijze waarop stelselmatige besmetting van dieren kan worden beïnvloed door de opneming van radionucliden in biologische stoffen en door chronische bestralingscondities verdient speciale aandacht.

- de migratie en retentie van radionucliden in een aantal gesteenten en bodemsorten die specifiek zijn voor de landen van de Gemeenschap (met name voor de transurannucliden en langlevende splijtingsprodukten);
- de overdracht van sedimenten van radionucliden, vrijgekomen in waterig milieu, en de mogelijke remobilisatie hiervan (met name de transurannucliden en langlevende splijtingsprodukten);
- de regionale verdeling en het gedrag van lang levende radionucliden (bijv. C-14, Tc-99, I-129) met speciale verwijzing naar de uitwisseling hiervan tussen verschillende componenten van het leefmilieu (bijv. uitwisseling tussen water- en landmilieu);
- de opneming van speciale radionucliden (bijv. Tc-99) door in water levende soorten, waaromtrent meer informatie is vereist;
- bestudering van de mogelijke synergistische effecten van radionucliden en conventionele verontreinigende stoffen die vrijkomen in het milieu, met speciale aandacht voor de opneming van radionucliden in voedselketens;
- de uitwisseling van C-14 en HTO tussen lucht- en land-milieu,
- de atmosferische dispersie- en neerslag-processen in stedelijke gebieden.

5. Vroege somatische effecten van ioniserende straling

Stralingsletsel treedt op op het moment van de bestraling. Alle daaruit voortvloeiende biologische effecten hangen hoofdzakelijk af van de snelle veranderingen die tijdens een buitengewoon korte periode, volgend op de energie-absorptie, optreden.

Uitvoerige kennis van deze gebeurtenissen zou ons in staat stellen het mechanisme van de stralingseffecten te begrijpen. Al vele jaren is het bekend dat vrije radicalen en hun reactieproducten een essentiële rol spelen in het vroege stadium van de radiologische schade, maar eerst recente technologische resultaten hebben het mogelijk gemaakt deze in biologisch materiaal te meten en te identificeren.

In betrekkelijk korte tijd werd grote vooruitgang geboekt en heden ten dage is men heel goed op de hoogte van de reactie van door straling geïnduceerde vrije radicalen met nucleïnezuren, die het voornaamste biologische doelwit vormen van straling.

Verdere studies op dit gebied zouden ons, indien zij op de juiste wijze worden gecoördineerd, een duidelijk inzicht geven in het primaire mechanisme van het stralingsletsel, wat van onschatbare waarde zou zijn voor een juist begrip van en de eventuele controle op de gevolgen van bestraling op levende materie.

De bestudering van de vroege cellulaire en weefseleffecten van stralingsletsel van interne of externe oorsprong zal worden geïntensiveerd wegens de toenemende betekenis hiervan in industrie, research en klinische geneeskunde.

Letsel dat wordt onderworpen aan een behandeling omvat hoofdzakelijk gelokaliseerd stralingsletsel en schade aan het lymfo-hemopoietische systeem. Deze pathogene studies zullen van fundamentele betekenis zijn voor de ontwikkeling van therapeutische methoden. Wegens de grote invloed van acute, subacute of chronische lokale stralingsletsels, zal speciale aandacht worden geschonken aan de bestudering van de werking, de prognose, de complicaties en de behandeling ervan. Al naar gelang de grote variëteit in de bestralingsmogelijkheden, welke zowel externe als interne bestraling omvatten, (absorptie of radioactief materiaal door ingestie, inademing of verwonding) kunnen

kunnen zij niet alleen de huid maar ook inwendige oppervlakten beïnvloeden zoals die van de slokdarm, de luchtpijp en vele andere organen.

Het bindweefsel en het vasculaire weefsel, dat vrijwel overal in het lichaam aanwezig is, verdient speciale aandacht voor wat betreft de mogelijke late effecten. De grote invloed van kankervorming na het gezingsproces is eveneens karakteristiek voor stralings verbrandingen. De pathogenese van deze letsels van de complicerende factoren en van het mechanisme en de kinetica van de cellulaire repopulatie, zal derhalve grondig worden bestudeerd. De studie zal tevens betrekking hebben op de karakteristieken van antigene veranderingen en mogelijke neoplastische alteraties van het beschadigde weefsel, de betekenis van de beschadiging voor het immuno - systeem en de specifieke problemen die zich voordoen bij toepassing van huid-transplantatie.

Vroege effecten van stralingsschade aan de bloedvormende organen door totale of subtotale lichaamsbestraling en de therapie van deze letsels werden in het kader van eerdere programma's bestudeerd en er werd aanzienlijke vooruitgang geboekt t.a.v. het begrip en de behandeling van het "beenmerg-syndroom". De vaststelling van het letsel en van regeneratiepotentieel van de bloedvormende functie aan de hand van bestaande diagnose-methoden is nog niet optimaal, met name wat betreft de diagnose van schade aan de stamcellen en aan bepaalde populaties van lymfocyten. Het gebruik van chromosomen-preparaten en andere verklikkers van stralingsletsel zal worden bestudeerd. Wat betreft de therapie, blijven verscheidene problemen de aandacht op eisen. Onlangs werden nieuwe stralingsbeschermers ontdekt die, wanneer zij nader worden onderzocht, waardevol kunnen zijn voor toepassing op de mens. Problemen van immunologische aard blijven een enorm struikelblok, hoewel resultaten op het gebied van de immunologie de mogelijkheid van mergtransplantaties bij de mens aanzienlijk hebben vergroot. Deze resultaten omvatten : de verwijdering van immunologisch reactieve lymfocyten uit de mergsuspensie (afscheiding van stamcellen). Aanmerkelijk verbeterd weefselonderzoek en cryopreservering van geslachtscellen (mergbanken) en de mogelijkheid om de immuunreactie, die een centrale rol speelt in het ziektebeeld van patiënten die behandeld worden met beenmergtransplantaat, te "manipuleren" (immuun-deficientie is de ernstigste late complicatie). Dit onderdeel van het onderzoekprogramma zal derhalve de nadruk leggen op immunologische problemen zoals :

- a. verdere verbetering van het paren (matching) van recent ontdekte weefselantigenen.
- b. scheiding en cryopreservering van stamcellen, met inbegrip van een gestandaardiseerde methoden tot vaststelling van de levensvatbaarheid ervan;
- c. bewaking van en verhoging van de immunreactie van de met beenmerg behandelde ontvanger, teneinde late complicaties te voorkomen (infecties en mogelijke door stralinge geïnduceerde neoplasie)

4. Late somatische effecten van ioniserende straling

Straling kan leiden tot twee soorten nadelige effecten en sommige hiervan kunnen eerst lang na de eerste bestraling manifest worden. Bij de ene soort, die gepaard gaat met de zgn. "stochastische effecten", hangt de frekwentie waarmee het effect optreedt op typische wijze af van de omvang van de stralingsdosis, maar de ernst van de effecten hangt in het algemeen niet af van de dosis. De inductie van kwaadaardig letsel vormt het belangrijkste voorbeeld van dit soort effecten.

Bij de andere soort, die gepaard gaat met "niet-stochastische effecten", is gewoonlijk geen significant letsel beneden een bepaalde "drempel" waarneembaar, maar de ernst van het effect dat dan ontstaat kan variëren met de omvang van de stralingsdosis. Het ontstaan van cataract of van verminderde vruchtbaarheid en de aantasting van orgaanfuncties of bloedvoorziening vormen veranderingen van dit type.

- Inductie van stochastische effecten

- a. Menselijke waarneming : kwaadaardige veranderingen tengevolge van straling zijn van bijzondere betekenis voor wat betreft de stralingsbescherming. De Commissie wijst derhalve met klem op de voortdurende noodzaak om de frekwentie vast te stellen waarmee de verschillende types van kwaadaardige gevolgen meer dan volgens de normale verwachting optreden bij bevolkingsgroepen die bij bekende dosisniveau's (om medische of andere redenen) zijn bestraald en die langdurige perioden liefst over meerdere decennia, uitgebreid werden gevolgd of kunnen worden gevolgd, gedurende welke verdere door straling geïnduceerde tumoren kunnen worden opgespoord. Speciale aandacht moet worden geschonken aan de dosimetrie, de duur en de doeltreffendheid van de follow-up, de vergelijkbaarheid van de controle-reeksen, de invloed van geslacht, leeftijd op het moment van de bestraling, de sterfte tengevolge van door straling veroorzaakte tumoren, die wijzen waarop de latente periode tussen de bestraling en de opsporing van tumoren varieert met de dosis of met andere factoren, de invloed van de kwaliteit van de straling (LET), het variëren van deze invloed (REE) met de dosis, en de vorm van de dosis-effect-relatie.

Groepen van patienten die aan herhaalde of uitgebreide diagnostische radiologische onderzoeken zijn onderworpen zullen worden bestudeerd, reikens, wanneer volledige gegevens, zoals de sterftekwaad-frekwentie tengevolge van kwaadaardige ziekten, beschikbaar zijn. Statistische studies van patienten die inwendige of uitwendige radiotherapie met beperkte dosis hadden ontvangen, met name bij de behandeling van niet-kwaadaardige ziekten, zouden extra risicoschattingen opleveren voor de inductie van kanker in belangrijke organen. De resultaten hiervan zullen slechts van betekenis zijn, indien controle-waarden kunnen worden vastgesteld voor de invloed van kanker bij patienten met dezelfde kwalen die niet met bestraling behandeld zijn. Dergelijke studies zouden tevens een leidraad moeten vormen voor de veiligheidseisen t.a.v. deze vormen van therapie. Soorgelijke studies betreffende de effecten van radiotherapie voor kwaadaardige ziekten, kunnen, ongeacht of deze alleen dan wel in combinatie met chemotherapie wordt toegepast, ook ertoe bijdragen de mogelijke latere gevolgen evenals de meest geschikte vorm van behandeling te bepalen, teneinde de frekwentie van dergelijke risico's tot een minimum te beperken. Bovendien kunnen deze studies licht werpen op mogelijk synergisme tussen straling en schemische agentia, of een grotere gevoeligheid voor stralingscarcinogenesis van speciale weefsels bij bepaalde ziekten aantonen.

- b. dierstudies : teneinde meer te weten te komen over het mechanisme van de kankerinductie zijn er vanzelfsprekend fundamentele experimentele studies nodig betreffende de aard van dit verschijnsel, en de frekwentie waarmee kwaadaardige veranderingen, met name door lage dosis en lage dosistempo's kunnen worden geïnduceerd. Deze gegevens kunnen de grondslag vormen voor geldige conclusies inzake de frekwentie van kwaadaardige veranderingen die zijn te verwachten, na de zelfs lagere doses bij beroepshalve of andere blootstelling aan straling.

Dosis-effect relaties bij lage doses, microdosimetrische studies, vergelijking van hoge en lage LET straling en van dosis verlening zullen worden uitgewerkt. Bij studies inzake gebeurtenissen na opname van radionucliden zal rekening worden gehouden met de volgende parameters : opname (door ingestie of inademing), stra-

lingskwaliteit biologische halveringstijd, verdeling over de organen, affiniteit voor speciale weefsels, gebrek aan homogeniteit van de afzetting, stofwisseling en uitscheiding en studies inzake het voordeel of eventueel nadeel van chelaatvormers. Tevens zal speciale nadruk worden gelegd op de variatie van factoren die het carcinoogene proces kunnen beïnvloeden.

Deze factoren omvatten leeftijd, geslacht, hormonen, virussen, het immuunsysteem en plaatselijke weefselreacties zoals endogene factoren en bepaalde aspecten van cocarcinogenesis en synergetische effecten zoals exogene factoren.

De juiste indentificatie van de bedreigde cellen en van de vroegtijdige en tussentijdige opeenvolging van gebeurtenissen tijdens de carcinogenesis zullen de ontwikkeling van nieuwe methoden noodzakelijk maken (inclusief biochemische en immunologische markers). Voorts dient het verband tussen mutagene en carcinoogene effecten te worden bepaald. Normalisatie van proefnemingen op dieren, van de tumor-nomenclatuur en de kwantificering van morfologische eindpunten zullen worden voortgezet.

- Inductie van niet-stochastische effecten

Wanneer men de procedures en de maximale doses voor stralingsbescherming wil vaststellen, is het van belang de soorten van niet-stochastische effecten te kennen, die door straling in de mens kunnen worden geïnduceerd, de ernst van deze verschillende effecten en het dosis-niveau waarop deze gemakkelijk kunnen ontstaan. Het is met name van belang, over gegevens te beschikken m.b.t. die effecten, die zouden kunnen worden geïnduceerd door doses oplopend tot enkele tienden van een sievert per jaar gedurende vele jaren of decennia.

Deze praktische eis geldt speciaal voor die weefsels of organen waarbij het percentage fatale kankerinducties per eenheid geabsorbeerde dosis waarschijnlijk laag is, aangezien voor weefsels als bot, huid en thyroïde de maximaal toelaatbare jaarlijkse dosis vermoedelijk minder door het mogelijke ontstaan van kwaadaardige ziekten dan door dat van schadelijke niet-stochastische veranderingen bepaald wordt.

Bij mens en dier zal gezocht worden naar gegevens betreffende de totaal geaccumuleerde dosis, afgegeven gedurende een belangrijk deel van de levensduur van een mens of dier, die dezelfde gevolgen teweeg kan brengen als één enkele dosis.

Inzicht in deze vraagstukken dient derhalve te worden verkregen door een herziening van zowel de effecten die ontstaan bij de mens als die welke proefondervindelijk bij dieren worden teweeggebracht. Bij mensen is het van belang de dosis na te gaan waarboven verschillende niet-stochastische effecten worden waargenomen, met name tijdens radiotherapie, waarbij geschikte dosisniveaus worden bereikt, maar waar mogelijk mede met inachtneming van de gevolgen van straling bij high LET en voorzover relevant die van de behandeling met radionucliden. Een studie van de pathogenese van deze effecten zal vermoedelijk licht werpen op de betekenis van herstel mechanismen.

In dit verband is het ook noodzakelijk de aard van alle mogelijke verschillen tussen de reacties van normale en zieke weefsels op bestraling vast te stellen. In vele gevallen mag verwacht worden dat de geaccumuleerde doses, die kwaadaardige veranderingen in een weefsel teweeg zullen brengen ook niet-kwaadaardige veranderingen zullen hebben veroorzaakt of geïnitieerd.

Elke interactie tussen de ontwikkeling van deze twee soorten van effecten of de invloed van niet-kwaadaardige veranderingen op de frekwentie van kanker is belangrijk.

De bestudering van het vroege stadium in de ontwikkeling van late niet-stochastische effecten kunnen ook belangrijk blijken te zijn voor de vaststelling van het vermoedelijke optreden van dergelijke late effecten.

Met betrekking tot het risico van elke vorm van bestraling tijdens zwangerschap, zullen teratogene effecten worden bestudeerd, met name voor wat betreft de volgende punten : mogelijk bestaan van een drempel, invloed van LET, mogelijk inactivering, herstel van embryonale cellen, verband tussen schade toegebracht aan afzonderlijke cellen van het embryo, belangrijke stoornissen in de ontwikkeling van het foetus, dosis/effect relatie in verschillende stadia van de embryonale ontwikkeling.

De frekwentie waarmee verschillende soorten van ontwikkelingsstoornissen (meestal van het zenuwstelsels) door straling bij mensen en bij elk experimenteel model worden geïnduceerd dienen zoveel mogelijk op elkaar te zijn afgestemd.

Een niet-specifieke verkorting van de levensduur door ioniserende straling blijft nog onzeker, maar het mechanisme hiervan dient te worden bestudeerd wanneer het bestaan hiervan proefondervindelijk wordt bewezen.

5. Genetische effecten van ioniserende straling

De studie van stralingseffecten op genetisch materiaal is van belang omdat stralingen de invloed van chromosomale syndromen en van erfelijke ziekten kunnen vergroten en omdat uitvoerige analyse nodig zijn van de ingewikkelde wegen via welke de bestraalde cel de invloed ondergaat pre-mutagene en pre-carcinogene letsels. De algemene doelstellingen in deze sector zijn het verstrekken van de informatie die nodig is om :

- aan de hand van de momenteel beschikbare methoden (directe schattingsmethoden en verdubbelingsdosis methode) de genetische schade vast te stellen die bij de mens door straling wordt teweeggebracht. De hiervoor vereiste kennis omvat schattingen betreffende de geboorte-frekwenties van genetische ziektes, bepaling van de waarden van verdubbelingsdoses en een evaluatie van de produktie van genetische afwijkingen per rad.
 - inzicht te krijgen in de factoren die de vaststelling van schade regelen, wijzigen of voorkomen. Het in het verleden verrichte onderzoek maakt thans de genetische en biochemische karakterisering van bepaalde processen van DNA-herstel in menselijke cellen mogelijk. Stimulering van het onderzoek naar de opheldering der mechanismen zou het niet alleen mogelijk maken deze werkzaamheden voort te zetten, maar uiteindelijk zou het nieuwe middelen verstrekken om de wisselwerking en effecten te voorspellen, om het verband vast te stellen tussen mutagenese en carcinogenese en om stralingsletsel te voorkomen of daartegen te beschermen. Het zou tevens de ontwikkeling van methoden voor de detectie van gevoelige individuen bespoedigen en wel met name van die individuen die heterozygoot zijn voor genetische ziekten, die gepaard gaan met een herstel-deficiëntie en die een grotere gevoeligheid hebben voor mutagene en carcinogene agentia.
- Om deze doelstellingen te bereiken is in het hieronder voorgestelde programma, waar mogelijk de nadruk gelegd op de directe analyse van menselijke systemen. Het gebruik van experimentele soorten wordt in alle gevallen waar geen betrouwbaar alternatief is, gehandhaafd.

- Vaststelling en analyse van genetische schade in eukaryonten

De mutaties van genen en aberraties van chromosomen, die spontaan bij mensen optreden, zijn een bron van narigheid e, verantwoordelijk voor een belangrijke deel van alle spontane miskramen, en bij voldragen baby's, van aangeboren misvormingen, geestelijke en lichamelijke afwijkingen.

De invloed van natuurlijk optreden erfelijke gebreken en ziekten bij menselijke bevolkingsgroepen werd door de UNSCEAR berekend op circa 1,0 % voor dominerende en X-gebonden ziekten, 0,1 % voor recessieve ziekten, 0,4 % voor chromosomale afwijkingen en 9,0 % voor geslachtsmisvorming, multifactoriële en onregelmatige geërfdde ziekten. Aangezien het bekend is dat bestraling mutaties en chromosomale anomalieën teweegbrengt is het derhalve van bijzonder belang de huidige methoden op het gebied van de detectie van genetische bestralingseffecten zoveel mogelijk te verbeteren en via een analyse van de inductie-mechanismen een lijst op te stellen van de verschillende factoren en omstandigheden die tot een uitbreiding van deze gevallen kunnen leiden.

Aangezien de menselijke systemen zich gewoonlijk niet lenen voor uitvoerige genetische analyses, zal een substantieel deel van het onderzoek worden uitgevoerd door middel van het gebruik van ander eukaryontisch materiaal, waar de soortgelijke chromosomale organisatie (DNA, histonen) en soortgelijke cellulaire organellen impliceren dat veel van de inductiemechanismen voor schade in de kern en in het cytoplasma identiek zijn met die van de mens. Het programma houdt in :

- a) de verbetering en ontwikkeling van analyse-systemen en proefondervindelijke methoden met vergroot oplossend vermogen voor de opsporing van door straling geïnduceerde alteraties zowel in lichaamscellen als kiemcellen van de mens,
- b) opheldering van het mechanisme dat leidt tot non-disjunctie van chromosomen en andere afwijkingen, met inbegrip van studie betr. het verband tussen structuur en gedrag van chromosomen (heterochromatine, synaptinemaal complex en satellietverbinding).
- c) studie van mogelijke verbanden tussen stralingsgevoeligheid, herstel- en segregatieve anomalieën,

- d) specifieke studies inzake de interacties en relaties tussen de biologische effecten van straling en andere omgevingsagentia,
- e) aan de hand van enkele speciale studies, opheldering van de effecten van bestraling op het mitochondriaal gemoon en de gevolgen hiervan voor het overleven van de cel.

- Dosis-effect relatie

Het is bijzonder moeilijk de relatie tussen dosis en effect bij de mens vast te stellen, aangezien onvoldoende menselijke gegevens beschikbaar zijn en aangezien de kwantitatieve extrapolatie van experimentele resultaten naar de mens ernstige problemen oplevert. Gezien de betekenis van dosis/effect relatie voor de vaststelling stralingsrisico omvat het programma :

- a) epidemiologische overzichten, die de aandacht richten op het verband tussen de ontvangen dosis, de frekwentie van afwijkingen bij lymphocyten en de biologische gevolgen op lange termijn van de bestraling. (aplasia bij kiemcellen en geïnduceerde effecten bij levend geboren en doodgeboren kinderen),
- b) bepaling van de in vivo kinetica van lymphocyten teneinde de interpretatie van doses van niet uniforme bestraling te vergemakelijken,
- c) onderzoeken met zoogdieren (voorzover mogelijk ook primaten); teneinde meer gegevens te verzamelen (zowel genetische als cytogenetische), die nuttig zullen zijn voor de kwantitatieve extrapolatie van genetische stralingsrisico's naar de mens,
- d) studies gericht op de beoordeling van de methoden en waarvan men zich be dient bij de vaststelling van het risico van de extrapolatie van lichaams-hypothesen, cellen naar kiemcellen en van experimentele soorten naar de mens
- e) studies inzake de inductie van mutaties in kiem cellen en lichaamscellen bij zeer lage doses en dosis tempo's en de ontwikkeling van technieken om dergelijke studies te vergemakkelijken.

- Biochemie en genetica van stralingsgevoeligheid en herstel

Als gevolg van het thans goed vorderende onderzoek naar de DNA-herstelwegen in micro-organismen, heeft het onderzoek dat gebruik maakt van menselijke cellen met mutaties die leiden tot hersteldeficiënties, aangetoond dat de mechanismen voor herstel van DNA-beschadiging van grote betekenis zijn voor de menselijke gezondheid. Verscheidene specifieke factoren tasten de herstel-mogelijkheden aan en een aantal erfelijke ziekten die vergezeld gaan van een grotere gevoeligheid voor straling en optreden van kanker, worden in verband gebracht met, afwijkingen in de DNA-herstel.

Een belangrijk deel van het voorgestelde onderzoek zal worden uitgevoerd aan systemen van zoogdieren en met name menselijke systemen, maar het gebruik van niet-zoogdier materiaal zal noodzakelijk zijn voor de diepte analyse en het simuleren van complexe biochemische en genetische mechanismen.

Het programma omvat :

- a) bestudering van de stralingsgevoeligheid van een groot aantal verschillende menselijke cellen (fibroblasten, lymphocyten, enz.) afkomstig zowel van een normale controlegroep als van vertegenwoordigers van menselijke ziekten met verhoogde gevoeligheid voor mutagene agentia uit het milieu. Waar mogelijk zal worden overgegaan tot een uitvoerige analyse van verschillen in stralingsgevoeligheid tussen individuen,
- b) identificatie en genetische en biochemische karakterisering van afwijkende celstammen van zoogdieren met uiteenlopende gevoeligheid en deficient wat betreft het herstel van DNA-schade,
- c) onderzoek naar de gedetailleerde enzymologie van DNA-herstelwegen (dit wordt momenteel het best bestudeerd bij micro-organismen waar de formele biochemie en genetica vaste voet hebben gekregen) en studies inzake de biochemische specificiteit en biologische betekenis van DNA-letsels in zoogdiersystemen. Dit zal het gebruik van proteïnen omvatten die specifieke beschadigingen onderkennen als analytische sondes voor het controleren van enzymatisch herstel en het verband beschadigingen en mutatie, recombinatie en chromosoom-afwijkingen,

- d) studies inzake mutagenese en de rol van constitutieve en induceerbare herstelwegen in zoogdierecellen. Bij dit deel van het programma zal tevens gebruik gemaakt worden gemaakt van verschillende onlangs in Drosophila geïsoleerde DNA-hersteldeficiente mutanten, die de mogelijkheid bieden de rol van DNA-herstelwegen bij de teweegbrenging van door straling geïnduceerde genetische schade in een eukaryontisch model-systeem te bestuderen,
- e) analyse van de relaties tussen DNA-herstel en hiermee verwante mechanismen en carciongenese.

6. Beoordeling van stralingsrisico's

De op het gebied van de stralingsbescherming gehanteerde begrippen kunnen in de Lid-Staten op verschillende manieren worden toegepast. Daarom is het noodzakelijk te trachten gemeenschappelijke methoden te ontwikkelen om de gevolgen van bestraling voor de mens en zijn omgeving zo nauwkeurig en objectief mogelijk vast te stellen.

De resultaten hiervan zijn ook van belang voor de besluitvorming inzake de bepaling van de plaats van vestiging van kernenergiecentrales en de keuze van de energievoorziening.

De nieuwe beginselen van optimalisatie en beperking inzake stralingsbescherming, die in 1977 door de ICRP werden aanbevolen, zijn gebaseerd op een schade- en risicobegrip en vereisen de vaststelling van realistische verhoudingen tussen de dosimetrische hoeveelheden en de genetische en carcinogene risico's. Er werden nieuwe dosimetrische hoeveelheden en begrippen ontwikkeld.

Hiervan noemen wij het effectieve dosis-equivalent en de dosis-equivalent-index voor de beschrijving van de individuele blootstelling en de collectieve dosis exposie, met het oog op de vaststelling van de schade toegebracht aan de collectieve gezondheid.

De praktische toepassing van deze nieuwe termen moet worden getest en het verband hiervan met meetbare kwantiteiten moet worden bepaald.

Er moeten drie categorieën van problemen worden bestudeerd.

De eerste is de vaststelling van de individuele en collectieve doses die het gevolg zijn van normale lozing van radioactieve stoffen en de vrijkomende van radioactieve stoffen in ongevalsituaties.

Deze vaststelling van de vrijgekomen doses moet berusten op gegevens verkregen door de beweging van radionucliden in het milieu, als beschreven onder 4.1.2., te bestuderen, en dient te leiden tot een betere bepaling van de dosisverdeling over de bevolking en de omvang van de collectieve dosis met inachtneming van de natuurlijke achtergrond.

Er zijn modellen vereist voor alle vermoedelijke toegangswegen tot de mens en zijn omgeving, waarbij de volledige splijtstofkringloop in aanmerking wordt genomen.

Wat betreft de optimalisatie op het gebied van de stralingsbescherming, die momenteel wordt bepleit, dient tevens rekening te worden gehouden met

alle risico's verbonden aan menselijke activiteiten waarbij gebruik gemaakt wordt van ioniserende straling of die bestraling beïnvloeden, zoals die welke medische toepassingen meebrengen en de technologisch veroorzaakte radioactiviteit. Het programma zal bestaan in een aantal opeenvolgende stadia, waarin de te bestuderen punten worden vastgesteld, de door werknemers en door het publiek ontvangen doses worden bepaald en onderzoek wordt gedaan naar mogelijke beschermende maatregelen en de daaraanverbonden kosten.

Het tweede probleem is het methodologische onderzoek inzake de vaststelling van de schade. Hierbij dient gebruik te worden gemaakt van gegevens verkregen d.m.v. experimenteel en epidemiologisch onderzoek, beschreven in de relevante sectoren van het programma.

Twee categorieën van problemen moeten worden bestudeerd.

In de eerste plaats die van de vaststelling van de schade in geval van bestraling met een gemiddeld of hoog bestralingsniveau, van toepassing bij een ongeval.

In de tweede plaats die welke verband houden met lage stralingsdoses, die met name belangrijk zijn voor alle beroepshalve blootgestelde personen.

Het derde probleem is de vaststelling van de economische en sociale gevolgen van bestraling. Dit is een nieuw onderwerp dat dient te worden ontwikkeld teneinde richtlijnen vast te stellen voor de optimalisatie van activiteiten op het gebied van stralingsbescherming, gebaseerd op het bereiken van "zo laag mogelijke niveau's als redelijkerwijze mogelijk is" onder voorwaarden die van toepassing zijn in Europa "as low reasonably achievable levels" (ALARA).

Scientific Documentation

This documentation represents in a certain sense a "raw material" which has been used during the preparation of the programme proposal itself and does not give a balanced view indicating the relative importance of its different sectors.

Most of its chapters are quite well reflected in the programme proposal. Others have only been used as background material at some stage of the preparation.

RADIATION DOSIMETRY AND ITS INTERPRETATION

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RADIATION DOSIMETRY AND ITS INTERPRETATION

1. Objectives of research activities

Application of regulations for radiation protection and research on effects of ionizing radiation can only be carried out properly if it is possible to determine absorbed dose and/or other exposure parameters and interpret them in terms of biological effects and the risks to which they give rise. Furthermore the directives of Euratom on Basic Standards for Radiation Protection require the measurements and recording of certain exposure data which should be carried out in a comparable manner within the Community.

Research in dosimetry within the future Radiation Protection Programme of the Commission of the European Communities must be based as well on experiences and results of previous programmes, as on new aspects in the assessment and control of radiation exposures which became evident during the last years. Priorities in dosimetry research of the current 5-years programme have anticipated to a large degree already new developments and tendencies. Evidently - and this since long time - the problems of low doses constitute a major preoccupation of dosimetry. Therefore important research projects which were started during the last 5-years period have to be continued or finalized, and new projects have to be initiated which take into account these new tendencies and requirements of radiation protection and radiation measurements.

The following facts have to be considered:

- Low level irradiation continues to raise many questions as far as risk estimates for exposure of the general public and occupational exposure are concerned. Earlier predictions have to be checked and dosimetric and methodologic questions be discussed in view of recent evidencies. The importance of this problem will certainly increase during the next future; it is a long term objective.
- In the last years some of the concepts for the judgement of radiation exposures have changed. The new principles of optimization and limitation in radiation protection, which have been recommended in 1977 by ICRP, are based on a risk-benefit concept. This requires the assessment of realistic relationships between dosimetric quantities and genetic and somatic risk, as a medium term objective.

- New dosimetric quantities and concepts have been developed in the last years. Among these are the terms effective dose equivalent and dose equivalent index for the description of individual exposure, and the terms collective dose and collective dose commitment for the assessment of the collective health detriment. The practical applicability of new concepts has to be tested and their relationship to measurable quantities has to be determined, an objective for the next future.
- In view of the energy situation, there is an urgent requirement to clarify the future exposure of the population from all steps of the nuclear fuel cycle, especially from fuel reprocessing and waste disposal, a requirement which raises many dosimetric problems, also a medium term objective.
- As 90% of the existing man-made exposure results from the application of X-rays and radionuclides in medicine, means for reduction have to be searched. This is an objective of still increasing importance, needing continuous long term support.

2. Priorities in dosimetry

From these considerations the following priority research subjects can be identified which require further investigation in support of the Radiation Protection Programme as a whole:

- Physical aspects of radiation effectiveness (Microdosimetry)
- Internal dosimetry
- Dosimetry in case of external irradiation
- Personal dosimetry and area monitoring
- Dosimetry of high-LET-radiation and neutrons.

Low level irradiation, of both low dose and low dose rate, is inherent in all of these subjects, forms a major part of them, or as in the case of microdosimetry is the main preoccupation.

A programme of continuing development and adaptation for all dosimetric methods - as has taken place in the past - is required to deal with changing needs of radiation protection. For this, some flexibility of approach is envisaged to tackle mission oriented problems or to carry out

exploratory studies of actual needs, or to develop new instruments, thus ensuring flexibility and capability for innovation in the future. Such problems could actually be seen in:

- Environmental dosimetry
- Exposure in medical diagnosis
- Biological dosimetry.

Obviously there are numerous dosimetric measurements and calculations necessary in the course of most research projects in a Radiation Protection Programme. But they are, as long as being routine measurements, in general not in need of any special Community effort. Uniformity and comparability, however, of dosimetric methods applied in other research projects and in practical radiation protection will be achieved and improved through:

- Intercomparison programmes.

The following pages will give a summarized description of the above mentioned subjects, indicating their relevance for radiation protection research, the state of the art and the actions to be taken, which are considered to be of high priority for the 1980-1984 programme of the Commission in Radiation Protection and especially its sector on "Radiation dosimetry and its interpretation".

3. Physical aspects of radiation effectiveness (microdosimetry)

3.1. Introduction

Various types of ionizing radiation, although sharing the same basic mechanisms of radiation absorption, show marked differences in the biological effectiveness. These differences are depending among other factors on spatial and temporal distributions of absorbed energy on a microscale and on the geometrical configuration of the biological target.

With classical dosimetry, it is not possible to understand the dose-effect relationships for different radiations and to predict the low dose effects which are the most important ones in any radiation protection concept because human data are scarcely available and animal experiments difficult to be performed. Microdosimetric considerations seem to deliver a quantitative description of the functional dependence of RBE on absorbed dose for many different biological endpoints. Recent radiobiological results have shown that the existing theoretical approaches have to be further developed, taking also into account radiation interactions at the molecular scale. It is to be expected that further investigation of the

physical aspects of radiation interactions will provide the necessary basis for the explanation of how the biological effectiveness finally depends on radiation quality.

3.2. Relevance for radiation protection

One of the most important goals of microdosimetrically oriented radiobiological models must be the prediction of risks for genetic and late somatic effects in human beings at such low doses, for which epidemiological studies can hardly reveal radiation effects unambiguously. Their application leads to the planning of more suitable animal experiments and reconsideration of existing human data. From the available results it cannot yet be decided whether the detriment from low doses and dose rates of low and high-LET-radiations have been over or under-estimated, and whether any changes are needed in quality factors, with all the impact that such changes might have on shielding design and personal dosimetry. It was e.g. suggested that for low doses and low energy neutrons the RBE might be substantially higher than presently assumed.

Another problem to be considered by microdosimetric concepts is the dose throughout a given tissue volume, and the procedure of averaging dose, important for risk assessment not only for occupational exposure but also for population exposure. As examples could be cited the inhalation of plutonium particulates which are translocated from the respiratory tract to the local thoracic lymph nodes. Is the lymph node dose to be averaged throughout the lymph node system or only in the locally affected lymph nodes; or, if a small number of particles of very high specific activity are deposited on the skin or on the epithelium of the airways of the lung how important is the very high local dose in the tissue volume immediately adjacent to the particles?

Microdosimetric techniques might permit the design of more appropriate instrumentation for radiation protection, than that presently existing in particular with regard to sensitivity, radiation characteristics and to a proper determination of the average quality factor.

3.3. Radiation mechanisms

Although the basic principles of microdosimetry apply to nearly all radiobiological effects, there are several radiation interactions and mechanisms which are not considered in the current mathematical concepts of microdosimetry. Biological effects of ionizing radiations originate from the transport of radiation energy in the biological tissue, the structural pattern of the emitted charged particles, the local and temporal development of the physico-chemical products, and the development of the primary biological mechanisms. Therefore radiobiological effects have to be understood as a result of interactions of the pattern of primary physico-chemical species with the biological sensitive matrix.

Therefore studies are necessary to extend the mathematical concepts of microdosimetry with the aim of taking into consideration radiation interactions on both, the molecular and the cellular levels. Possibly synergisms of radiation with other environmental factors could be included.

Biochemical interactions may account for a large part of the total radiation effect on the cell (the most familiar example being chromosome aberrations). Because of their importance as regards the kinetics of the radiation effect, additional information might be obtained by the use of appropriate analytical techniques: variation of particle range in relation to interaction distance, variation of radiation quality, split-dose experiments, simulation using Monte Carlo calculations.

Basic prerequisites for these biological studies are most complete information on the physical radiation interaction of low energy photons, stimulated Auger electron emission, low and high energy neutrons, and high energy ions. In particular, experiments and calculations are needed on track structures, clusters of energy deposition, the spatial distribution of the secondary physico-chemical species and the possible temporal correlation between them. The necessary

techniques also include dosimetry and spectroscopy and the calculation of slowing down spectra for the type of radiation employed.

3.4. Practical applications

Experimental studies on the clustering of energy deposition on molecular levels require the development of new microdosimetric facilities. Also studies on new tissue equivalent materials for specific radiations should be performed. In addition, the possibility of application of microdosimetric counters for area monitoring should be investigated.

Due to the close correlation between radiation induced alterations of the genetic information of cells and other radiation damages there is considerable interest in investigating energy deposition in the DNA and in chromosomes. Therefore methods should be developed which are appropriate for studying the frequency distribution of ionizing events on the nanometer-scale.

The development of new tissue equivalent materials is desirable for low LET radiations, high energy ions, and π -mesons. Experimental microdosimetry of low LET radiations and energetic ions is unnecessarily impeded by the use of detector-wall materials and gas fillings, which originally were developed as tissue equivalent materials for mixed neutron-gamma-radiation. However, if the essential interactions of these radiations, e.g. photoelectric effect, Compton effect, and stopping power, are taken into account, the opportunities for using raw materials and filling gases are considerably less restricted.

Extension of existing systems to practical application requires improvement of available instrumentation and methods as well as the design of more simple devices which are sufficiently cheap and allow reliable measurements. In this respect intercomparison of proportional counters should be encouraged together with handling procedures.

4. Internal dosimetry

4.1. Improvement of dosimetric models and metabolic studies

In order to evaluate properly the hazards from incorporated radionuclides it will be necessary to improve dosimetric models describing in a somewhat simplified fashion the metabolism of nuclides within the body, their excretion and their time dependence. Of particular interest are the dosimetric models of different organs such as the lung, the gut and the bone.

4.1.1. The lung model

The lung model is divided into two distinct parts: deposition and retention. Existing problems with the deposition model concern the nasopharyngeal deposition of large particles which could be released into the environment from a serious reactor accident. More information is required about the deposition in the human respiratory tract of particles of known size distribution. The retention model is based on very little human evidence and specific problems concern retention and absorption of large particles in the nasopharyngeal region, retention and clearance of particles from the alveolar region, movement of particles from the alveolar region to the respiratory lymphnodes, retention in the respiratory lymphnodes, solubility of compounds in lung fluids, allocation of compounds to the three solubility classifications.

4.1.2. The gut model

In the gut model the main area of uncertainty concerns the absorption into the body from the small intestine. This is of particular importance for biologically incorporated actinides and some rare earths.

4.1.3. The bone model

Considerable uncertainties exist for the bone model, e.g. the identification and exact endosteal location of the cells responsible for the development of osteosarcomas, the surface area of the endosteum, the rate of burial of surface deposits in young people and in adults, and the unknown movement of plutonium from the bone into the marrow.

The improvements of these models will have to be based on careful biological studies of the actual mechanisms of the inhalation and ingestion processes, and their dependence on the chemical composition or the size of the particulate of the radionuclide, as well as the connection between excretion levels and the retention and distribution of various radionuclides in the body. Other factors, detailed in other sectors of the Programme, will have to be considered, as e.g. pharmaceutical methods of improving excretion.

4.2. Inhomogeneities within organs and within cells

Not only are various isotopes concentrated more strongly in different organs of the body, for example radioactive iodine which concentrates in the thyroid gland, but in some instances there may be inhomogeneities in the distribution within organs and cells.

One important example as for occupational as for population exposure which has already been underlined is the dose calculation in case of inhaled radioactive particulates and their translocation to the lymphnode system.

On the cellular level are isotopes such as tritium and ^{125}I of interest which are producing high local energy concentrations as e.g. in the decay by Auger-electron emission.

Knowledge of the biological effects arising from the inhomogeneities and highly localized doses is very limited and more research work in this area is required. Such research will need to make use of the results of microdosimetric investigations and models of dose/effect relationships.

4.3. Methods of assessing body burdens of radionuclides

Attempts to improve methods for the detection of radionuclides within the body are necessary, especially in view of the increasing practical importance of actinides. Some research is required into the development of better whole-body counting equipment, with emphasis on improved calibration and on the exact location of the radioactivity within the body. Development aimed at increasing the speed, accuracy and the use of improved models of urine and fecal analysis for excreted isotopes should be encouraged.

5. Dosimetry in case of external irradiation

External irradiation can give rise to quite inhomogeneous dose distribution or to partial body irradiation making it sometimes difficult to establish the dose in irradiated organs or tissues under risk. The dose distribution in the body depends on a number of factors including:

- the geometrical location of the irradiated organs in the body,
- the density distribution and the atomic composition of these organs and of the overlying tissue,
- the field characteristics of the radiation, i.e. the distribution in energy and direction of its different components.

Physical and calculational methods have to be improved in order to relate these factors more accurately to the organ dose. In particular the local variation of absorbed dose at an interface of materials of different density or different atomic composition requires attention.

The transposition of a homogeneous phantom dose in terms of inhomogeneous tissue is still at the development stage. Quite a number of still practicable correction processes exist and need further improvement. In addition, the phantom technology involved requires further development.

Monte Carlo calculations and other transport theory methods have been used with great success to determine doses which cannot be ascertained experimentally either because of the inaccessibility of certain special areas in organs or because of the unacceptable length of time required for measurements. However, there is a considerable need to further update transport calculations in terms of both its mathematical aspects and the availability of physical input data. Sufficiently accurate cross sections are still not available in many areas of radiological protection and radiation therapy.

There is considerable need to reconsider dosimetry procedures in case of partial body irradiation. In accidents normally only parts of the body, most frequently hands and forearms, have been irradiated, and correct treatment depends largely on information about the level of irradiation of different parts of the body.

6. Personal dosimetry and area monitoring

Following the recommendations in recent ICRP publications the revision of radiation protection standards needs to be backed up by research into methods aimed at applying and evaluating these recommendations.

The changes in the basic principles contained in the recommendation, in particular the change-over from the critical organ to the whole body as the basis for risk assessment, involve far-reaching dosimetric adjustments.

6.1. Metrological problems

The new standards introduce the concept of "effective dose equivalent" in assessing the radiation dose in applied radiation protection. The aim here is - solely for purposes of radiation protection - to simplify, with the aid of this quantity, the procedure involved in determining the effective radiation dose resulting from external and internal exposure. However, the possibilities of realization of the effective dose equivalent and the dose equivalent index or other alternative concepts need to be investigated in view of their use and application in practice.

Realizing that effective dose equivalent cannot be measured directly, it has been suggested that for external radiations the deep dose equivalent index for penetrating radiation and the shallow dose equivalent index for exposure of the skin might constitute a reasonably accurate approximation of the corresponding effective dose equivalent. Yet so far no practicable technique exists to derive these two secondary quantities experimentally, even though they are easier to calculate than effective dose equivalent.

Applied radiation protection faces the task of determining the relationships between these or other new quantities and those used up to now and for which measurement apparatus and measurement techniques exist. The relationships must be determined both theoretically and experimentally for all radiation fields that exist in practice.

Such tests constitute the basis for the introduction of new concepts into practice and for the formulation of recommendations as to the construction of appropriate measuring devices.

6.2. Practical problems of personal dosimetry and area monitoring

6.2.1. Improvement of measuring devices

Excellent work in the improvement of instrumentation has been done in the past and considerable progress has been made. Yet quite some difficulties still exist, e.g. in neutron personal and area dosimetry, as described later under point 7. In general, improvement of the energy response - a problem that again became evident in the execution of intercomparisons - and development of better selectivity for different types of radiation as in mixed fields are urgent problems. Only when the contribution to the total dose equivalent resulting from various radiation types can be determined with an adequate reliability will it be possible to ensure that dose limits are strictly observed.

For all types of radiation it will be desirable to develop measurement techniques and apparatus which permit dose determination in the quantities referred to in 6.1. - independently of the energy or energy distribution of the radiation - over the widest possible ranges.

6.2.2. Accidental dosimetry

Uniform strategies and measurement techniques must be available in order to measure the radiation dose in the event of accidents or catastrophies. Research into dosimeters for use in case of radiation accidents was undertaken since some time. In view of its results it appears necessary to consider new developments and to undertake again the related tests and intercomparisons, which can best be ensured by European cooperation.

6.2.3. Analysis of exposure conditions

One important aspect for the assessment of occupational radiation risk is the analysis of the radiological situation and its correlation with the reading of radiation protection instrumentation and the working conditions. This could be cleared up by dosimetric experiments combined with appropriate inquiries.

6.2.4. Calibration methods

Correct calibration of the measurement instruments in radiation protection with respect to the ranges of energy, absorbed dose, and absorbed dose rate encountered in practice is an essential prerequisite for reliable dose measurement.

This presupposes well-defined standard radiation fields. Some work especially in view of their practical importance is necessary with respect to low and high energy monoenergetic photon radiation, beta radiation, and neutron radiation of low and intermediate energies. In order to determine the standard fields precisely it is necessary to establish their spectral composition as accurately as possible, because e.g. in the case of neutron radiation even small amounts of other energies or other radiation types can seriously distort calibration.

7. Dosimetry of high-LET-radiation and neutrons

Concerted support is necessary to achieve data on high-LET-radiations including neutrons of selected energies of practical importance. Although many physical data and measuring methods for neutrons have been published or elaborated in recent years, methods in personal neutron dosimetry as well as for neutron and high-LET-dosimetry for radiobiological experiments are not yet completely satisfactory. It is an urgent problem to collect and evaluate data that will enable a general consensus to be reached on neutron dosimetry itself. In this area also intercomparisons require a continuing effort, since those which have been carried out have revealed unexpected discrepancies in dosimetry procedures and accuracy.

Among the urgent objectives are the following:

- In radiobiological experiments with neutrons there exists always an unavoidable gamma component which must be measured separately. The accuracy and precision of mixed beam dosimetry still suffers from instrumental shortcomings. This includes practical problems, such as detector design, as well as theoretical problems with respect to detector response.
- Theoretical and experimental basic data for simulating ion track structure have to be completed. Existing radiation transport codes must be adapted, the input data sets as e.g. cross sections for delta-ray emission extended and improved, and finally the results verified experimentally.

- Neutron personal and area dosimetry still suffers from insufficient instrumentation. Especially albedo track etch dosimeters need further consideration.
- New regulations in radiation protection necessitates the knowledge of organ doses for relevant standardized exposure situations. The latter have to be gained from extensive field studies.
- Organ doses and derived quantities, like e.g. the effective dose equivalent referred to in 6.1., have to be computed by neutron and mixed field transport codes and backed up by experiments.

7.1. Practical beam dosimetry

Radiation protection research on the consequences of neutron exposure is widely based on radiobiological experiments with neutrons and mixed radiations. For this purpose high accuracy of dosimetry has to be achieved which needs further improvement of existing techniques and of currently applied parameters.

A problem is still the exact determination, theoretically or experimentally, of the detector sensitivities used in mixed field dosimetry, as e.g. the neutron sensitivity of G.M.-counters.

For the determination of the dose distribution over the body, which is generally derived from measurements with TE ionization chambers, it is further of importance to ascertain the effective point of measurement for neutron beams of different energies.

7.2. Development of instruments and methods

It has already been mentioned that efforts are still required to attain the precision and accuracy needed in personal and - even more - in radiobiological dosimetry of mixed radiation fields and especially for the determination of low neutron doses in the presence of high gamma doses.

The development of detectors having a response proportional to dose equivalent for a wide range of radiation quality should be encouraged.

In general, as a consequence of recent discussions on revision of neutron quality factors, new dosimetric techniques have to be considered, the sensitivity of which to neutrons would be sufficiently high to cope with the ranges of doses of interest.

7.3. Dosimetry intercomparisons

Recent coordinated programmes of neutron dosimetry intercomparisons have proved the existence of large discrepancies between the values of absorbed dose determined by different participating groups. Such discrepancies cannot be explained as being only due to difference in the values of the physical parameters utilized for the dose determination. Instrumental and procedural inconsistencies are, therefore, still present, which can hinder the correct transfer of information from one laboratory to another. Since the refinement of dosimetry techniques and procedures is an iterative process, more intercomparisons have to be planned for the immediate future. This type of studies requires a well organized cooperation and a continuing coordination effort.

7.4. Calibration and standardization

Primary calibration of instruments is performed at national or regional standardization laboratories. To facilitate however the comparison of dosimetric results at different laboratories, the use of a uniform transfer instrumentation represents the most appropriate way to perform local instrument calibration. A continuing coordinated effort should be oriented, therefore, to the standardization of suitable transfer instruments and to the definition of operating procedures.

7.5. Relevant physical data and dose computations

For the evaluation of risks of exposure of man to mixed neutron gamma fields, it will be finally of importance to assess the dose distribution in the different essential tissues and organs.

This dose distribution will be determined by a large number of factors including:

- a) the radiation quality of the incident mixed beam,
- b) the geometrical position of organs such as bone-marrow, gastro-intestinal tract, lungs, and
- c) the atomic composition of the organs in which the energy is deposited and the atomic composition of the overlying tissue.

For special conditions it seems possible to perform irradiation experiments by means of suitable phantoms. In other cases however, mixed field transport calculations can provide all necessary information.

In this context, information has to be obtained about fluence-to-kerma factors and the attenuation characteristics of the different tissues. The dose variations at an interface of materials of different atomic composition deserve attention.

As cooperative biological research projects have indicated, no uniform utilization of physical data relevant to dosimetry with ionization chambers has been achieved so far. In order to eliminate such a discrepancy for dosimetric results, sufficient effort has to be directed to a critical evaluation of the available data and, if necessary, to the theoretical and/or experimental verification of selected values of the mean energy for ionization, stopping powers and kerma ratios for the various materials of interest. In addition, the influence of the chemical and physical characteristics on the response of the dosimeter deserves still careful experimental and theoretical investigation. Coordination in this area is expected to be most fruitful.

8. Environmental dosimetry

A more realistic estimate should be made of the dose to the public resulting from natural radioactivity and enhanced natural exposure. This forms part of the proper assessment of the risk from man-made radiation sources.

In view of an assessment of the man-made enhancement of natural radiation exposure, experimental and theoretical studies on the gamma-radiation from natural radionuclides in building materials and within houses should lead to an evaluation of the effective dose equivalent. It needs the development of methods for the measurement of Radon exhalation from walls and for the activity concentration of Radon and daughters in room air as well as studies about the radioactive disequilibrium and the fraction of unattached Radon daughter atoms in room air (comparison with outside air, influence of room ventilation ...). The dose distribution in the lung from inhaled ^{222}Rn - and ^{220}Rn -daughters under normal living conditions has to be evaluated and the potential lung cancer risk from this source be estimated and compared with the lung cancer risk from other sources (smoking, air pollution). The same type of research would apply to studies about other technologically enhanced sources of natural radiation.

9. Exposure in medical diagnosis

Exposure in medical diagnosis makes the greatest contribution of any man-made radiation source to the general population. Research in dosimetry will aim at reducing the non-essential dose from this exposure while maintaining the quality of the diagnostic information. It will also examine the usefulness of such data for epidemiological studies of radiation effects.

A detailed description is given under the section "late somatic effects of ionizing radiation", however, a few important subjects should be listed here in view of eliminating unnecessary medical and dental irradiation:

- Evaluation of the effective genetic and somatic dose from all diagnostic investigations with X-rays and radionuclides, as far as they are still unknown.
- Development of methods for risk-benefit analysis and optimization of diagnostic procedures; comparison with alternative, non-radiation methods (mass screening of the lung, mammography, thyroid diagnostics).
- Compilation of data about the frequency of typical diagnostic investigations and the corresponding doses to relevant organs and tissues.
- System analysis of X-ray installations (including analysis of image quality) with respect to a reduction of the exposure of patients.
- Improvement and multinational harmonization of the quality control of X-ray installations used for diagnostic purposes.

Medical exposure reduction appears achievable without loss of diagnostic or therapeutic benefits, and - in some cases - may result in enhanced benefits.

10. Biological dosimetry

Biological dosimetry might be used in case of accidents to provide important additional information on the effective dose received. Unfortunately the existing methods have not proved entirely sufficient in certain accidental situations. Research is needed on the development and improvement of reliable biological dosimetric methods and on the influence of a wide range of dose rates and non-uniform spatial dose distributions on the biological indicators.

The importance of such methods also for risk estimates at the occupational level is underlined by the fact that cytogenetic studies on human peripheral blood lymphocytes have revealed increased chromosome aberration yields after in vivo exposure to relatively low doses being consistent with a linear dose response.

In addition it might be useful to devote special attention to the use of in vitro biological systems as "quality dependent" dosimeters.

11. Intercomparisons

Cooperative research in radiation protection depends largely on the degree of standardization of experimental methods and materials. A number of dosimetric intercomparisons have therefore been carried out, for instance on personal dosimeters and whole body counters, on X-ray and neutron dosimetry. All these intercomparisons revealed quite a number of imperfections in experimental arrangements, differences in the basic values used to determine the absorbed dose, and discrepancies in dosimetry procedures. The intercomparisons induced a considerable improvement in dosimetry procedures, and increased the accuracy and reproducibility of the measurements.

Generally accepted procedures for measuring ionizing radiations and for uniformly interpreting them are the objectives of such intercomparisons, they are a requirement for effective communication between individuals concerned with radiation protection. Similarly, information on the various radiation measurement techniques which are appropriate for different purposes, will result from these intercomparisons. They have to be repeated at regular intervals and wherever necessary, new intercomparisons have to be initiated.

This is the case in personal dosimetry as in many other areas such as X-ray and neutron dosimetry or microdosimetry, for which the technical methods of measurement and interpretation differ between the laboratories concerned and generally accepted criteria for the estimates of precision and uncertainties of the results obtained do not exist. Thus the execution of an intercomparison with its three levels:

- organization of a practical intercomparison for different significant radiations,
- formulation of recommendations for the methods of calibration, measurement, and interpretation and
- collection and evaluation of relevant basic data and improvement of practical measurements,

will greatly facilitate European collaboration.

12. Implementation

Research on dosimetry, in contrast to other research sectors in radiation protection, is generally widely dispersed within small research units all

over the Community. Therefore particular attention has been given to coordination and cooperation throughout the sector, which will even be strengthened in the future.

Four methods of implementation have proved to be efficient and economic in the past years and need to be continued:

- the bringing together of dispersed efforts through collaborative programmes, dovetailing of projects and joint planning arrangements,
- the providing of an adequate structure for approaching difficult dosimetry problems of high priority by common efforts,
- the exchange of information and experience, through study group meetings, such as those of the European dosimetry group, and through symposia and workshops,
- the intensified communication between scientists through arrangement of working visits.

Thus unnecessary redundancy of work will be avoided and the most economic use of the limited and dispersed capacities be achieved.

BEHAVIOUR AND CONTROL OF RADIONUCLIDES IN THE ENVIRONMENT

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BEHAVIOUR AND CONTROL OF RADIONUCLIDES IN THE ENVIRONMENT

TERRESTRIAL AND SURFACE - WATER ENVIRONMENT.

1. Significance of the subject.

Power from nuclear fission is regarded as the major non fossil source of energy Europe can rely on for the near future. During the near-term (till 1985) and mid-term (till 2000) periods emphasis will be placed on overcoming the technological and environmental problems inhibiting expansion of highly utilizable existing nuclear systems, notably light water reactors. In the mid- and long-term (beyond 2000) periods, major emphasis will be placed on the successful development of fusion and breeder nuclear reactors.

The hazards of large scale nuclear fission operations (mining and milling included as new uranium resources will have to be explored to satisfy the Community demand) have to be evaluated and a research programme involved in radioactive contamination of the environment must consequently supply the necessary information required by such an evaluation. Such research is an essential input to the assessment of the radiation detriment of routine activities and events which result in the release of radioactive materials to the environment.

Radiation protection principles have been recently reviewed and based on defined risk levels to be compared with those derived from other human activities. This principle as well as those of optimization and limitation of the dose require, as input data for proper evaluation of the collective doses, a detailed knowledge of the variability of the dose received from natural sources within space, time and the various groups of the population in absence of byproducts of human technological activities.

International authorities have recently recognized the importance of studies concerning natural radiation in the environment in view of its

growing role as a reference point for the evaluation of the impact into the environment of both nuclear and conventional power plants as well as of many commercial products of large consumption and containing amounts of natural radioactivity.

Mankind has always been exposed to ionizing radiation from various natural sources and in some situations the exposure to natural radiation may be enhanced as a result of technological developments. The activities to be retained in the framework of this sector are :

- the coal fired power plants ;
- the use of phosphate fertilizers.

In the nuclear power industry, important costs are incurred for radiation protection, reflecting the present public concern more than present risk estimates. The optimal conditions for the implementation of nuclear industry have to be determined taking into account the individual and collective doses in respect of normal discharges of nuclear power installations and in the event of an accident.

The exposure of individuals in function of a large number of factors which are related to the way of life and use of the environment. The restriction of the exposure which is caused by the release of radioactive materials into the environment depends on :

- Radioecological studies applied to future electro-nuclear sites (critical pathways, etc.) ;
- The control of releases of gaseous and liquid effluents ;
- The control of disposals of solid wastes (one strong argument against further proliferation of nuclear installations is the exacting technological implication to safely handle the high radioactive waste materials. The wastes must be isolated from the biosphere for extended periods of time) ;
- Appropriate arrangements for reducing the probability of accidents (The development of the fast breeder reactor would impose added environmental risks).

The assessments require the use of models of various degrees of complexity representing the movement of radioactive materials through

the environment. These models have to take into account the nature and the physical and chemical forms of the radioactive materials together with the kind of release involved. These data must be made available for the authorities responsible for authorizing the discharge of radioactive materials and for defining acceptable limits for such discharges into the environment. These authorizations should be based on preoperational studies which should be carried out at an early stage of the project.

Over the past years, the information developed has been mainly based on experiences from the testing of nuclear devices and experiments in controlled conditions. In the future more attention must be paid to solving the problems of radioactive contamination by peace-time applications. The ecological diversity of the natural environment entails a considerable variability in the critical pathways of transfer. This variability exists both in space and in time, and the process of transfer cannot be understood from a simple extrapolation of the results obtained from short-term experiments conducted in the laboratory. Consequently, although many data have already been accumulated on the behaviour of several radionuclides, several gaps remain and some of the data which are available need to be improved in reliability.

Nuclear energy which is now competitive, may assume a more important share of the installed energy capacity, and in a near future, might be for Europe one of the main sources of electricity and of the needed industrial power. Moreover, the rapidly expanding use of atomic energy for peaceful uses resulted in a variety of types of industrial and scientific activities and research work which also may result in releases of radioactivity to the environment. In addition to the radionuclides, nuclear energy is responsible of other types of pollution (heat, noise, etc.). Industrial complexes, frequently situated on the same sites, also produce non radioactive pollutants and heat. Consequently, ecosystems are frequently polluted simultaneously by nuclear and non-nuclear pollutants and cumulative or even synergistic effects must be looked for.

The European long-term strategy might be based on a symbiotic combination of breeders and advanced converter reactors based on both, the uranium and thorium cycles. The potential health and environmental im-

pact of these new technologies must be carefully evaluated before their introduction.

Commercial application of fusion, from the point of view of health and environmental effects, will differ from fission in :

- the absence of volatile fission products and transuranic elements ;
- a greater amount of neutron-induced radioactivity ;
- a larger tritium production.

The potential health and environmental impact must be evaluated and the necessary knowledge collected to ensure that technologists have pertinent information in order to give an adequate consideration to environmental problems. As a result of accidents, radioactive material could be released in the form of aerosols, gaseous and liquid effluents (release of activated products from the coolant system, and tritium from the reactor).

The main purposes of the environmental studies to be done in the framework of the next programme are :

- The study and the verification of the "predicted" contamination levels ;
- the detection of "unforeseen" ways of contamination ;
- the determination of "improved criteria" for prediction of future levels based on an "acceptable risk", examining the conventional risks the society accepts and matching the nuclear risk to these ;
- the "reduction" or "limination" of radionuclide transfer in accident situations ;
- the research on "cumulative" or "synergetic" effects.

Care must be taken to ensure that objective information regarding the radiological impact of increasing nuclear activities is dissipated to the competent authorities and to the European Public.

2. Sources of human exposure.

2.1. Natural radiation.

The various natural radiation sources include external sources (cosmic rays, radioactive substances in the ground and in some building materials) and internal sources (radioactive substances in the body). Some practices may raise the level of exposure to natural background radiation :

- use of certain materials
- consumption of water and food in which the concentration of natural elements is high.

Different actions are needed to enlarge the state of our knowledge :

- accurate measurements of the natural background ;
- evaluation of the role of the diet in the contamination of man ;
- study of the pathways of natural radionuclides from the source to man.

2.2. Technologically enhanced exposures.

Practices that may increase the level of exposure from the natural background radiation include the consumption of water and foodstuffs in which the concentration of natural radionuclides is generally high because of their origin or has been enhanced. Little emphasis has been placed on the health, physical or environmental perspectives of the enhanced radioactivity caused by various industrial operations. The following practices may contribute to an increased transfer of radionuclides.

2.2.1. Production and use of fertilizers and by-products.

The mining and milling of phosphate rock annually extract several thousands of Curies of radium-226, uranium-238 and thorium-232. Approximately 60% of the activity remains in the slime and sand tailings after beneficiation. Care must be taken to prevent unnecessary release of slime material to streams and rivers. Increased emphasis is warranted on assessing the potential impact of recycling the by-products slag and gypsum in building materials.

The use of phosphate fertilizers may increase the level of exposure from the natural background radiation through the consumption of water and foodstuffs in which the concentration of natural radionuclides is unusually high.

2.2.2. Coal-fired power plants.

The EPA-regulation for coal-fired power plants is 1% ash release to the atmosphere. Assuming 1 and 2 ppm of respectively uranium and thorium

in the coal, the population dose for a same amount of energy delivered would be higher from the coal plant than from a pressurized or boiling water reactor. The prospect of a greater impact of the coal-fired power plants in energy production emphasizes the necessity of more accurate assessments of their radiological health hazards, as the major pathways of exposure of the population are through inhalation of airborne flyash and by consumption of foodstuffs contaminated by radium-226 leached from the dumped flyash. Attention must be paid to assess the potential environmental hazard of recycling the flyash (e.g. road constructions).

2.3. Power generation from nuclear fission.

2.3.1. Mining, milling and fuel fabrication.

The mining and milling of uranium are redistribute the naturally radioactive material and may produce a measurable radiological impact in the immediate vicinity. In the case of mining, attention is focussed on radon. The predominant long term environmental problem faced in uranium ore milling centers on mill tailings. Radium-226 and thorium-232 contained in the tailings are readily available for dispersion (leaching, wind blown). The radioactive materials discharged to the environment from fuel fabrication are limited due to the removal of the solid uranium compounds from airborne wastes.

2.3.2. Reactor operations.

The type and quantity of radioactive materials released from reactors depends on the reactor type and on the specific waste processing system utilized. Radionuclides may reach the environment through either the gaseous (krypton and xenon isotopes, carbon-14, sulphur-35, iodine-131, and -129, tritium) or liquid (tritium, fission and activation products) effluent streams.

More details are given in chapter 3.

.3.3. Fuel reprocessing

Waste processing to prevent large releases of radioactivity to the environment at reprocessing plants is a complex task. The gaseous and volatile fission products (iodine-131, tritium, krypton, xenon, ruthenium, tellurium and caesium) are separated from the fuel. The aqueous wastes, containing almost all of the fission products are concentrated and stored. The release of radioactive materials from the fuel reprocessing plant depends upon the type of fuel, irradiation history, cooling time and the specific waste processing system. More detailed information is given in chapter 3.

.3.4. Waste disposal

Large quantities of radioactive wastes, different among themselves in chemical composition and characteristics are produced (activation products, fission products, actinides). Among the various alternatives for the ultimate high activity waste disposal, (geological, sea-bed, ice sheet, extra terrestrial, nuclear transmutation) geological disposal seems the most realistic solution. In such a system different barriers can be identified: the waste is solidified, incorporated in glass or other materials resisting dissolution, surrounded by a canister and deposited in deep geological layers. One of the major hazards is that the waste comes into touch with water. Radionuclides which are mobile might then reach the biosphere in a relative short time interval (technetium-99, iodine-129). The potential hazard of the waste, without taking into account its retention by the geological barrier, for a period up to 300 years after disposal, is mainly determined by the fission products strontium-90, yttrium-90 and caesium-137. Between 100 and 30 000 years after disposal, the actinides plutonium-240, americium-241, neptunium-237, curium-246, americium-243, neptunium-239 and plutonium-239 cause the highest potential hazard. After 10 000 years, uranium, thorium and radium and their daughter nuclides neptunium-237, uranium-233, thorium-229, radium-226, actinium-225, radium-226 and lead-210 together with the long lived fission products technetium-99 and iodine-129 determine the potential

hazard. Moreover, some recent studies have shown that alpha-contaminated low level radioactive waste could play an important role in environmental pollution in the case of failure of the barriers surrounding it. More information is needed on the ecological behaviour of the different nuclides listed above after emergence from deep buried sites.

3. GASEOUS AND LIQUID EFFLUENTS OF NUCLEAR POWER PLANTS AND REPROCESSING PLANTS

Over the coming years, and notwithstanding all safety measures taken, the further extension of nuclear facilities for energy production and other nuclear methodologies may result in increased releases of radioactive substances to the biosphere. Accidents in and around nuclear plants also may be the cause of severe contamination of the environment. With regard to the potential hazard for man, three routes of differing importance may be distinguished: a) an increased level of external radiation, b) internal contamination by the inhalation of radioactive gases and aerosols and c) internal contamination by the ingestion of radioactively contaminated drinking water and alimentary products. A study of the general behaviour of the radiocontaminants in the environment, their possible accumulation in specific compartments and their ultimate incorporation in the food chain is the final goal of this programme. A simplified scheme of the transfer of the radiocontaminants in the environment is depicted in figure 1. It describes the pathways of the radiocontaminants to a particular compartment of the ecosystem. The final dose to man following a release of radioactive material to the atmosphere may be strongly influenced by processes occurring at the earth's surface.

3.1. Gaseous effluents.

The gaseous effluents discharged from nuclear power stations contain small amounts of fission and activation products produced in the reactor, i.e. noble gases (e.g. krypton and xenon isotopes, argon-41), halogens (iodine-131), particulates, tritium and carbon-14. The discharge levels of iodine-131 are generally very low and only a small fraction (usually less than 1%) of the iodine released in gaseous effluents is bound to particulates, most of it being in gaseous form. The discharge by nuclear power stations of aerosols with longer half-lives (more than 4 weeks) is in general extremely low. Their radioactivity results from both, activation and fission products. The following activation products have been identified: sulphur-35, chromium-51,

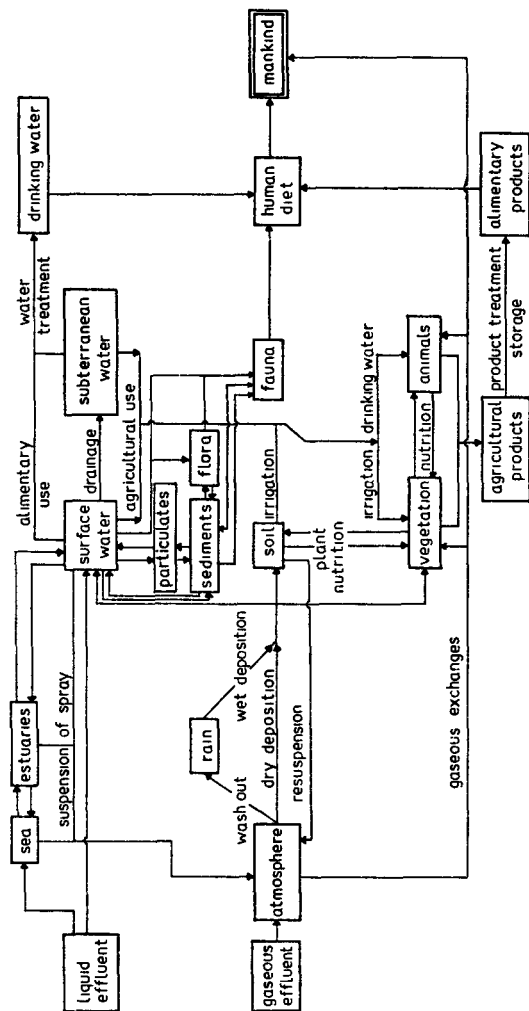


Figure 1: Simplified scheme of the transfer of nuclides in the environment (for easier reference, "vegetation" and "animals" are used for the terrestrial ecosystem, "flora" and "fauna" for the surface-water ecosystem, i.e. all non-marine water ecosystems (surface water, lakes, estuaries, brackish water)).

manganese-54, cobalt-57, -58 and -60, iron -59, zinc-65, silver-110^m, antimony-122, -124 and -125. The fission products identified were zirconium-95, niobium-95, ruthenium-103, -104 and -106, tellurium-123^m, caesium-134 and -137, barium-140, lanthanum-140, cerium-140 and -144. However, the radionuclide composition can vary considerably from one power station to another, and even in the same station from year to year. The amount of tritium discharged by light water and gascooled reactors is very low; the discharge from heavy water reactors is much higher. The discharges of carbon-14 have aroused interest in recent years since its long half-life and its biological behaviour will lead to accumulation in the environment. In pressurized water reactors only a small fraction of the quantity released is in the CO₂ form (most of it as methane and/or other hydrocarbons) whereas in boiling water reactors over 95% is discharged as CO₂.

For reprocessing plants, the gaseous effluents contain fission and to a lesser extent activation products, Krypton-85 is the only noble gas of interest. The alpha-active aerosols contain a variety of uranic and transuranic nuclides. Experience with a particular U.S. plant showed a dominance of plutonium components. Nuclides contributing to the beta-active aerosols are strontium-90, zirconium-95, niobium-95, ruthenium-106, antimony-125, caesium-134 and -137 and cerium-144. The tritium discharge usually amounts to 1% of the krypton-85 activity discharged implying 10 to 20% of the tritium inventory of the fuel. The iodine-131 release is largely due to the reprocessing of small quantities of fuel with a short cooling time. The discharge of iodine-129, due to its very long half-life, became of interest for its possible accumulation in the environment. Very few carbon-14 discharge data of reprocessing plants are available.

3.2. Liquid effluents

About 40 different radionuclides can be identified in the liquid effluents of nuclear power stations. Both the amount as well as the composition of the liquid releases may vary considerably, even among stations of the same type. The most prevalent fission products are caesium-134 and -137, strontium-89 and -90; the most predominant activation products are cobalt-58 and -60, antimony-124, chromium-51, manganese-54 and sulphur-35. The tritium release of pressurized water reactors depends on the fuel cladding material but tends to be

higher than for boiling water and gascooled reactors. For re-processing plants, the alpha activity charge of the liquid effluents is due to a variety of uranic and transuranic nuclides, and in recent years a dominance of plutonium components and an appreciable contribution of americium-241. The beta activity is due to tritium (only 10 to 25% of the sum-total of tritium discharges in liquid and gaseous effluents is to the atmosphere) and to some specific nuclides: strontium-90, ruthenium-106, caesium-134 and -137 and cerium-144.

Research on the importance for radiation protection of the various radionuclides mentioned is needed and must be evaluated frequently. It is evident that accurate knowledge of the composition of the effluents of nuclear power plants and reprocessing plants is essential to this purpose.

4. ATMOSPHERIC DISPERSION, DEPOSITION AND RESUSPENSION OF RADIONUCLIDES; EXCHANGE OF GASES AND VAPOURS

4.1. Atmospheric dispersion

The main objective of these studies is to prepare agreed dispersion models including important specific effects as plume rise, coastal effects, transport over water, topographical effects, terrain roughness, urban heating, building effects, variation of mixing height, mesoscale problems, time variant meteorology, lateral spreading. Deposition, washout and resuspension are considered in more detail in this programme.

4.2. Deposition of radionuclides

Deposition reduces airborne concentrations and consequently moderates the inhalation dose, but the deposited material may contribute to the external radiation field or may enter the food chain resulting in an ingestion dose. Deposition of particles to vegetation and soil has been studied in laboratory and small-scale field experiments. On a larger scale, weapons fall-out, industrial contaminants, and other substances found in the atmosphere provide further information. The most complete information available concerns grass and similar surfaces. Results obtained show that particle size has an important influence on aerosol behaviour. These studies also show the importance of Brownian diffusion in the deposition of particles below 0.1 μm . Interception by leaf hairs, impaction and sedimentation dominate for

particles larger than $1\text{ }\mu\text{m}$. Between 0.1 and $1.0\text{ }\mu\text{m}$ none of these processes is very effective and the deposition velocity has a minimum. Behaviour in this region is important as coagulation causes condensation aerosols to accumulate in this size range.

Few direct measurements of dry deposition of particles to grass and crops have been made, but some estimates based on measurements using artificial surfaces are available. There is a need for further research on deposition to crops in field conditions including investigation of the effect of particle size. Direct measurements of deposition to forest are even more sparse. The large vertical extent of the foliage and horizontal variations in density may deflect tracer plumes. Therefore, large distant releases of tracer, with sampling of a large volume of forest canopy would be necessary to obtain reliable deposition data.

Practically nothing is known of the deposition of particles in urban areas. In view of the large population which might be exposed to external and internal radiation resulting from deposition in such areas, work in this difficult area should be encouraged.

Few measurements deal with deposition of particles at sea. First results suggest that the sea should differ little from other smooth surfaces as a sink for particles although bounce-off is unlikely to be significant at sea. Around Europe deposition from the air to the sea is unlikely to be of radiological significance: much more activity is discharged to the sea, via pipelines or rivers, than into the air and liquid effluents control concentrations in marine ecosystems.

4.3. Resuspension of radionuclides

The deposited material may also be resuspended and give rise to inhalation exposure long after an incident. Most of the reported observations of resuspension were made in arid rural conditions with sparse vegetation, and may have no relevance in Europe. Concentrations of resuspended particles decline with time after deposition, and increase with wind speed, but estimates of the rate of increase vary markedly. Resuspended material is mostly attached to soil particles having an aerodynamic median diameter around $10\text{ }\mu\text{m}$. Only a few percent of the aerosol may be respirable. Possible resuspension factors for material incorporated in the soil may be estimated from the concentration of soil dust in air and the concentration of contaminant in the surface soil.

A large fraction of the population lives in towns or cities, but there is practically no knowledge of the behaviour of particulate material in urban situations. Resuspension due to traffic and the residence time of particles on roads and building surfaces may have an important effect on potential doses to a large number of people.

It has been known for several decades that the sea-spray aerosol is significant in the geochemical cycles of chlorine, sulphur and other major components in seawater. The deposition of sea spray may be very large close to coasts. Measurements suggest that the major components are present in the aerosol in the same ratios as in seawater. If this were true for radioactive waste, the great dilution offered by the sea would usually render sea spray insignificant. However, trace element studies show that the material transported by air may be enriched relative to sea water.

Enrichment is also observed in samples of surface film material collected from the sea by suitable techniques, and the surface film of the sea is thought to be the source of the enrichment elements in rain and dry deposition samples. Enrichments of the surface film may be physical or chemical in origin, or may involve biological processes. It is important to determine whether this effect applies to radioactive waste discharged to sea. The enrichment factor may differ for each nuclide, may depend on chemical treatment before discharge and may vary with time and dilution after discharge.

Measurements of air concentrations of radionuclides near marine discharge points, and a study of the mechanism of transfer from the sea to the atmosphere are necessary to provide an understanding of this process. Transport from intertidal mud flats and salt marshes may also be significant.

Points of general relevance to resuspension from surfaces in Europe are:

- contamination of the terrestrial ecosystem by suspension from the sea surface,
- resuspension in urban areas, and the change with time following deposition,
- resuspension from grassland and soil as a function of soil moisture and local microclimate,

- resuspension by rain and mechanical disturbances,
- the relationship between the size distributions of airborne and surface particles and their associated activity distributions,
- penetration of actinides and other contaminants into soil, and the influence of chemical form,
- resuspension due to biological activity

4.4. Exchange of gases and vapours.

There is a good general understanding of the physical processes which control the exchange of gases at surfaces. However, the conditions at the surface may be of great importance, are different for each gas and must be investigated experimentally. Soluble gases are readily absorbed by wet soils and by the mesophyll surface within leaves, and their uptake may be controlled by the degree of opening of the stomata, while insoluble gases (e.g. HT, CO) may be absorbed by soil micro-organisms.

Iodine-129, $^{14}\text{CO}_2$, HT and THO currently attract a lot of interest in the nuclear environment and need further study. The rapid deposition of I_2 would probably limit its mean lifetime in the atmosphere to 1 or 2 days. However, the attachment of I_2 to particles and the release or conversion of some of the I_2 to CH_3I or HOI must be taken into account. Particulate iodine and CH_3I deposit very slowly, stay airborne longer and may travel further before deposition. The deposition characteristics of HOI are not well known. $^{14}\text{CO}_2$ may gain access to food chains from the atmosphere by photosynthesis, but a substantial proportion may subsequently be respired so that uptake must be considered partially reversible. A good deal is already known of the rate of assimilation but a careful desk study would be necessary to decide whether this knowledge is adequate to predict the consequences of a release of $^{14}\text{CO}_2$.

Tritiated water vapour is readily exchanged with the water phase in soil or plant tissue, and the uptake is almost entirely reversible. This return to the atmosphere over a period of days or weeks makes the prediction of doses difficult. A computer study is probably necessary. Further work on the incorporation of tritium into the organic matter of crops during a short exposure may also be necessary.

The exchange of gases and vapours at sea surfaces has been studied by geochemists and oceanographers concerned with the cycles of the major atmospheric gases, and with the supply of oxygen to marine biota. Depletion of atmospheric plumes of HTO , I_2 , $^{14}\text{CO}_2$ may be appreciable and the desorption of these gases from the sea near

discharge points may be significant. Surveys near known sites of marine discharges and a study of information available in the literature should indicate whether further work is necessary in this area.

5. RADIONUCLIDE TRANSFER IN ECOSYSTEMS

5.1. General aspects

The pathways of the cycling of radiocontaminants in the environment after release in gaseous or liquid effluents of nuclear power stations and reprocessing plants are outlined in figure 1. The accumulation of a radiocontaminant in a specific compartment is described by the "transfer coefficient" of the radionuclide, relating the concentration in the "acceptor" (e.g. water biota, plants, animals) to the concentration in the "donor" (e.g. water, soils, plants). This transfer, however, is a complex function determined by many parameters characterizing both the donor and acceptor system. The most important of these parameters are treated in the following sections on freshwater and terrestrial ecosystems.

The commonly used expression "transfer coefficient" (or in some documents concentration factor or concentration ratio) is misleading. It indeed suggests that the transfer is characterized by a constant ratio between the concentration of the radionuclide in acceptor and donor. Such a constant ratio does not exist. The term transfer coefficient only means that for an "average donor" and an "average acceptor" under "average conditions" within an ecosystem, the concentration ratio of the radiocontaminant between acceptor and donor scatters.

The transfer of a radiocontaminant from one compartment to another only can be described by a "transfer function". At any moment t during the transfer process, a transfer coefficient TC_t from the donor to the acceptor can be computed. The value of TC_t is a function of the parameters characterizing donor and acceptor e.g. physicochemical form and availability of the radionuclide, the specific activity of the radiocontaminant, the specific properties of donor and acceptor, the environmental conditions governing the interaction between donor and acceptor, etc. The transfer function TF is a function of the change of TC_t with time

characterizing in a dynamic way the accumulation of the radio-contaminant in the acceptor. In many cases, only parts of the acceptor are incorporated in the food chain and at harvest a TC_t for the edible parts must be computed. In case of internal radiation assessments, a TC_t for specific sensitive organs is needed.

The use of complex experimental ecosystems can be useful for modelling if one takes into account the scaling errors and proportions and if the error computations are adapted. Multi-disciplinary research is needed for predictions on the behaviour of the radionuclides in the ecosystems. The results of field experiments should indicate where fundamental knowledge about transfer processes is lacking and must stimulate laboratory research. It is evident that a better knowledge of the behaviour of radionuclides in the environment will allow a more precise predictive modelling, both on short-term and still more on a long-term base. Even for the more common radionuclides of strontium, caesium, iodine, manganese, cobalt and tritium, hypothetical models for transfer processes are still needed.

5.2. Surface-water ecosystems

Some contrasts exist between surface-water and marine ecosystems. Relatively simple relationships such as a higher isotopic dilution in sea-water can explain the lower transfer coefficient e.g. for caesium and strontium isotopes observed in marine organisms. The different transfer coefficients of plutonium and americium in both environments are not clearly understood. The Am/Pu ratio in marine algae is variable, and sometimes plutonium is thought to be more available in the marine than in the surface-water environment although in other instances the contrary is concluded.

The surface-water bodies are highly variable in composition and physical characteristics, much more than for the marine environment. This increases the necessity of their study also as a function of the local conditions in which transfer of radiocontaminants and ecosystem irradiation could eventually occur (e.g. transition from surface-water to marine ecosystem). Abiotic and biotic factors may influence the radioecological evaluations of transfer processes and irradiation in the surface-water ecosystems.

5.2.1. Abiotic factors

5.2.1.1. Physicochemistry of the radionuclides.

A growing awareness exists on the importance of the physico-chemical form in which the nuclides exist in the surface-water environment, and the resulting transfer coefficients. Lack of knowledge of the significant parameters e.g. for americium, with a corresponding lack of understanding of the variability of results. The role of the physico-chemical form together with the concentration of the stable elements or the non-isotopic carrier element must be known better to explain the wide variation in transfer coefficients, reported in different natural water bodies for caesium, cobalt, manganese and strontium isotopes. This could increase the knowledge of the mechanisms operating in similar organisms for similar radionuclides but in different environmental situations.

5.2.1.2. Influence of temperature, other pollutants, eutrophication

Particular attention must be paid to the increase of environmental temperature of subtropical species. These species normally live quite close to their upper temperature limits and they thus could experience severe changes in their metabolic patterns and reproductive capacities with relatively moderate increase of ambient temperature. The metabolic interaction of metals is also worthwhile to be studied from the point of view of transfer of radionuclides. Most studies on the biological surface-water cycling of transuranics are done in eutrophic lakes; little information is available for meso- or oligotrophic conditions.

5.2.1.3. Sediments and substrates as reservoir for radionuclides and as irradiation sources

The role of sediments as a trap for most of the radionuclides has been known for a long time. In contrast with this, there is a serious lack of knowledge on the potential mobilizing effect of biota and of long-term changes in water quality etc., on this reservoir of nuclides. No experimental studies have been done in Europe on the influence of microbiological actions on the radionuclides trapped in river sediments. Together with the microbiological action, but probably some orders of magnitude less important, are the effects of the benthic (semi) macro-organisms on the solubilization and transfer of sedimented radio-

activity. Notwithstanding the important amount of nuclides trapped, a controversy exists about the importance of these quantities as a source for transfer of radiocontaminants. Thus, caesium, americium and plutonium in sediments are sometimes quoted as being of low importance.

Resuspension from the sediments has been recognized as important for the availability of americium and plutonium resulting in higher Pu-levels in benthic food chains. Radiation coming from the sediments is believed potentially important for benthic communities and its role has been taken into account in modelling. The transition from surface-water to marine conditions is a complex situation. Little is known about the role of salinity and temperature in the equilibria of the radionuclides between water, sediments and suspended materials. It would be worthwhile to study whether the desorption phenomena found e.g. for caesium during this transition is also valid for other radionuclides. There is thus inadequate knowledge on the behaviour of radionuclides in sediments and on its importance for the biota for the surface-water environment, particularly in such systems that could be compared with European situations.

5.2.2. Biotic factors

5.2.2.1. Transfer coefficients

Notwithstanding the extensive research done on transfer processes in a number of species under laboratory conditions, a serious lack still subsists on research done on species with a very broad ecological distribution. Such organisms might be used as indicators for plutonium and deserve attention in comparative studies to allow sound generalization of transfer mechanisms in different environmental conditions. The necessity in some exceptional instances to prevent the biological invasion of burials of low level waste e.g. by water fowl and insects must be stressed.

Tritium has to be evaluated in the perspective of fusion energy. Radium has particularly variable transfer coefficients, which are still not well enough understood to make valid general predictions for doses to the population. The long-term build-up of iodine-129 in surface-water biota is not well enough documented; and the parallelism with data on iodine-131 has to be controlled.

The number of caesium-studies is substantial. It is thus striking to note that more information is needed on the important role that fungi could play in the caesium-distributions in flood plains, and on the fundamental mechanisms that are responsible for the very different caesium-concentrations in different plant species. High plutonium concentration coefficients have been mentioned in phytoplankton (5000 times the water value), with a decrease of one order of magnitude for each further tropic level.

5.2.2.2. Metabolic aspects of transfer phenomena

It is evident that every transfer of radionuclides has to be understood through the metabolism and general physiology of the organisms concerned. Furthermore the variations in transfer and their possible peak values, will be governed by the same mechanisms. The distribution of the radionuclides in the organisms has to be understood carefully to avoid serious under-estimations of the dose to organs, especially with alpha-emitters, and the understanding of the interaction of metabolism and growth processes will allow some sound interpretations as well as more valid predictions.

5.2.2.3. Food and direct uptake of radionuclides

The ionic epithelial regulation, and homeostatic functions through direct uptake of minerals from the water are responsible for part of the transfer of radionuclides in surface-water organisms, but data about the relationship between feeding rate and transfer coefficients are confusing.

The feeding habits and formation of faecal pellets of zooplankton can remove some nuclides (plutonium) from surface waters (summer stratification) in contrast with other nuclides (caesium) which remain constant. In general, the knowledge of regulation mechanisms is not broadly enough established to allow safe predictions on radiocontamination levels in new situations and more fundamentally oriented research will help to overcome this lack.

5.3. Terrestrial ecosystems

5.3.1. Soil-Plant Transfer of Radionuclides

The transfer between soil and plant is a complex function which is determined by many variables. In the majority of situations a realistic transfer coefficient which is far below any "worst case value" can be applied. For special conditions (determined by climate, type of soil, type of crop and type of production) higher transfer factors will be required.

An approach to obtain values for the transfer from soil to plant which are reliable and can be used in (dose rate) calculations should include:

- a. Assessment of the uptake under standard (well defined and well controlled) conditions.
- b. Assessment of how the transfer is influenced by different types of crops, climates, soils, agricultural techniques, etc.

Two modes of contamination must be distinguished: an acute contamination (accidents; accidental releases) and chronic contamination (contaminated water for irrigation purposes; aerosol deposition etc.). In the case of an acute contamination, the major characteristic of the situation is a gradual shift towards establishment of a dynamic equilibrium between the contaminant and the soil. In the case of a chronic contamination, several fractions of the radionuclide all characterized by different availabilities for uptake by the plant, are simultaneously present.

In setting up the assessment of the uptake by plants, soil and plant parameters must be considered:

5.3.1.1. Soil physico-chemical aspects

a) Concentration of the contaminants

For small concentration ranges of a contaminant in soil, the uptake by the plant is usually proportional to the concentration. In no way, however, an extrapolation over a concentration range of 10^2 may be used. This means that the contaminant concentration in an experiment must be of the same order of magnitude as the expected contamination level.

b) Concentration of other contaminants and nutrient elements.

Both the presence of chemically identical stable isotopes and of chemically related elements influence the uptake of radioactive elements. This is a very interesting phenomenon; studies of this interaction, however, often do not consider concentration ranges that exist in soils, but those ones which were of interest from a physiological point of view.

c) Chemical status

The chemical form considerably influences the uptake of radiocontaminants. Specially the uptake from releases of soluble radiocontaminants may be much higher than for equilibrium conditions. This fact is usually recognized; the opposite effect, i.e. the gradual conversion of the more soluble form into the less soluble thermodynamically defined equilibrium form is often overlooked. In fact it is incorrect to base annual intakes on experiments with soluble forms. Some aspects of particular importance are more extensively treated below.

- Chelating agents.

Because of the formation of a more soluble complex with some organic compounds, e.g. with chelating agents, the uptake may be higher than expected. Some of these complexes must be expected to be rather stable and to be built up in the course of time (mainly via the cycle: uptake by the roots - release to soil by decomposition of roots after harvesting). However, this does not mean that all types of organic additions to a soil can be considered as representative for increased uptake due to chelation.

Additions of humic acid or fulvic acid increase the uptake in general; additions like citric acid, ethylenediamine tetra acetate (EDTA), diethylene triamine penta acetate (DTPA), and nitrilotriacetate (NTA) cause a severe increase of the uptake, but they do, however, not represent normal situations. The influence of NTA in sewage sludge must be considered.

- Organic matter content

The organic matter content in most soils ranges from 0.5 to 15% carbon, and buffers the concentration of radiocontaminants in the liquid phase to a certain degree. Consequently the uptake from

soils with less than 0.5% carbon, pure sand, quarts, etc. will be higher than from normal soils. The latter substrates do not represent normal conditions.

- pH

Productive soils have a pH between 5.2 and 7.3. Especially for metals of the second group, like strontium, the pH influences the uptake considerably. For scientific reasons the pH range 5.2 - 7.3 is often extended in experiments, providing higher and/or lower transfer coefficients.

Because the productivity of a soil of say pH = 4.5, is low, they hardly contribute to the mean diet. (In some isolated mountain districts they may do).

- pF

The water content of the soil continuously changes as a result of total evapotranspiration, drainage and rain and/or irrigation intensity. This induces changes in chemical concentrations in the soil solution, and repeated wetting and drying cycles strongly influence the biological activity in the soil. Normal pF values are from 1.8 to 3.5 although for growth of vegetables on peat soil a pF value of 1 is still representative. In case of irrigation, the suspended particles may have distinct influences on the transfer coefficient for different isotopes. The exchanges between water and solid material will be particularly important between flood plains and rivers (unexpected heterogeneity in uptake of caesium-137 is seen in plants in areas subject to flooding).

- Redox potential

For many of the transition metals and actinides the chemical form depends mainly on the redox potential. For pH = 7, the redox potential in moist soils ranges from 400 to 700 mV. Under anaerobic conditions, for instance a flooded rice soil, the redox potential may drop to 100 versus -200 mV.

5.3.1.2. Plant physiological aspects

The most important plant physiological factors affecting the transfer function of a radiocontaminant from the soil to the plant and the transfer coefficient to the edible parts of the crop at harvest are the growth-rate-determining parameters and the specific morphology of the edible parts.

a) Growth-rate-determining parameters

- Parameters affecting the root environment

All soil physico-chemical aspects dealt with in the previous paragraphs do influence the processes occurring at the soil-root interphase. The influence of factors affecting root morphology and extension of the root system as plant properties, temperature and humidity gradients as well as O_2/CO_2 ratios must be considered. Rhizosphere effects, i.e. exudation by the root of low molecular weight organic compounds acting as natural chelates, by which the physicochemical form of the radiocontaminant is changed, must be evaluated.

- Parameters affecting the shoot environment

Climatological parameters connected with the geographical location of the contaminated area such as temperature and humidity of the air, day length, light intensity and gaseous composition of the air directly influence the photosynthate production.

The transpiration coefficient of the crop (TrC), i.e. the amount of water required per kg dry matter produced, is influenced by these growth-rate-determining factors. Under field conditions, the TrC varies between 300 and 500; for extremely dry conditions it may go down to 100, for conditions of optimum water supply it may go up to 500. Care must be taken to ensure that uptake experiments carried out in lysimeters, greenhouses or growth chambers are representative for field conditions.

b) Morphology of the edible parts

As stated before, the final contamination of the food chain will largely depend on the transfer coefficient of the edible parts at harvest. The influence of the specific morphology of the consumed plant parts, e.g. leaf or fruit vegetables, tubers, cereals, green cattle fodder, on the contamination of the human diet must be considered carefully.

This knowledge might be of value for the reduction of the transfer of radionuclides from contaminated agricultural land to man (see sector 6 "Evaluation of radiation risk")

c) Synergistic effects

Synergism, in this context, can be described as a significantly increased uptake because of an unexpected interaction between variables controlling the uptake. As an example, the Zn-Cd and Cd-Se interactions indicate in some instances a decrease in toxicity with an increase in transfer. Such interactions could become increasingly important in conditions of fluctuating solute concentrations (e.g. in discontinuous irrigation) in which periodic drying must affect the binding of different metals to the organic substrate in the soil and to the soil minerals, in a differing way.

Screening for unexpected interactions is a time consuming process without any guarantee for success. For the time being the best approach is probably to be alert on synergistic effects and to start with thorough investigations if obvious indications for synergism are remarked.

(Antagonistic effects are treated in chapter 6 as a means to reduce the transfer from contaminated agricultural land to man).

d) Toxicity of radiocontaminants

Some radiocontaminants may have a twofold influence on the vegetation, namely a radiological impact and a chemical toxicity. Especially for technetium-99, toxic effects were reported which may be of chemical nature. Given the high mobility of technetium-99 in the geosphere (see chapter 2.3.4. Waste disposal), further investigations to elucidate this and similar aspects are warranted.

5.3.1.3. Conclusion

The available literature contains few observations made under strictly representative conditions. Consequently they can only be used for indicative purposes, but not for (dose rate) calculations or legislative procedures. It is recommended therefore to develop a thorough and consistent programme for the assessment of transfer coefficients and transfer functions.

5.3.2. Plant-Animal Transfer of Radionuclides

The number of experiments in which the transfer of radionuclides from plants to animals has been studied, is quite limited. The practice usually followed is to study in the laboratory uptake and retention of a particular nuclide by the plant on the one hand and to investigate resorption, metabolism secretion and excretion by the animal on the other. When the results thus obtained are combined, a fair idea of the situation in the field when contaminated plants are actually ingested by an animal, is usually acquired. However, the characteristic features of a particular ecological situation may not have been taken into consideration, and these may modify profoundly, in either direction, the value of the transfer of a radionuclide from plants to animals, from the value obtained in the laboratory. Metabolization of a radionuclide by the plant and subsequent ingestion of this plant by an animal may have a similar effect on the transfer of the radionuclide.

Examples of these situations are the importance of plant-base contamination in the transfer of strontium and cesium deposited on old pastures (a situation which is not encountered in the laboratory), the accumulation of cesium and other radionuclides by perennial plants such as lichen, the changes in retention time of deposited radionuclides when cows actually graze the pasture, etc. In the following paragraphs, the contamination of animals, of their edible tissues and organs, and of their secretion products such as milk, by the incorporation of radionuclides in their food is considered.

In the preceding discussion of contamination problems in surface-water and terrestrial ecosystems, the procedure adopted has been a discussion of the parameters which are of importance for the transfer of radionuclides. A similar discussion in relation to the contamination of domestic animals has turned out not to be very satisfactory for various reasons. Since the number of relevant radionuclides is limited, it was felt that, for the sake of clarity, a discussion of the problems related to the transfer of a particular radionuclide or group of radionuclides rather than a discussion of the different parameters, was to be preferred.

5.3.2.1. Tritium and Carbon-14

Tritium metabolism in animals has been studied almost exclusively on the basis of administration of tritium as THO. Many valuable data have been accumulated on the turnover of tritium in the body water pool and on its incorporation into organic molecules. In contrast to this, very little experimental information is available on the behaviour of organically bound tritium in the animal organism, particularly after metabolization of tritium by the plant and its subsequent uptake by the animal. The Commission's current research programme on tritium metabolism in plants and animals will produce a great deal of very valuable information. It may be expected, however, that some important gaps of knowledge remain to be filled.

Experimental results suggest that important differences in the metabolism of ingested organically bound tritium exist between monogastric (man, pig) and polygastric (cow) animals; limited information is available on the incorporation and turnover of organically bound tritium, ingested by young, growing animals through their feed.

When the ^{14}C containing organic plant material is being ingested by animals, the animal organism will contain progressively more ^{14}C labelled organic molecules. A great deal of knowledge has been accumulated in physiological research on the precursor-product relationships, both qualitatively and quantitatively, for the synthesis of carbohydrates, proteins and fatty substances, and also of specific molecules such as hormones. So far, experiments have not been carried out which were specifically designed

to elucidate the transfer of ^{14}C by plants on the utilization by the animal organism of the ^{14}C which has become available in the course of digestive processes. Differences between monogastric and polygastric animals in this respect should be taken into account. Information, based on practical conditions, is not available on the question of whether any differences exist in the time required for complete labelling of organic milk constituents to occur. The same is true for possible differences in turnover of ^{14}C in muscular tissue of growing and mature animals.

5.3.2.2. Activation products

Generally speaking, very few experiments have been carried out on the transfer of activation products from plants to animals. Many activation products are known in animal physiology as trace elements, and information on their metabolism is usually available. However, this information is based on laboratory experiments in most cases which have been carried out in order to clarify problems of animal physiology such as the minimum daily requirements of the trace element under consideration. When the daily intake satisfies the requirements of the animal, and deficiencies have not been noticed there is little incentive to study in detail the complex effects of the chemical form of an element in the plant and of subsequent digestive processes in the animal (ruminal fermentation in polygastric animals and digestive hydrolysis at low pH in monogastric animals) on the final availability of the element for intestinal absorption. This may explain why the information on the metabolism of trace elements is incomplete in certain aspects.

Cobalt is a vitally important trace element because it is an integral constituent of vitamin B_{12} which contains about 4,5% of cobalt. This vitamin is synthesized in the rumen in relative large quantities, part of which is absorbed. The liver is the main storage organ, but vitamin B_{12} is found also in other organs and tissues (muscles), and it is capable of crossing the placental barrier. It may be expected that the absorption of cobalt by the animal is related to the amount ingested in the fodder. However, limited information is available on its quantitative aspects, particularly in

the case that pasture contains only just enough cobalt to meet a daily intake of 1-2 mg of cobalt, required by cattle. Cobalt secretion in milk is low and variable. It centers around 1 microgram per liter under normal conditions.

Zinc is widely distributed in plant and animal tissues. It is a functional component of several enzyme systems and occurs in all living cells. Its absorption by the intestinal tract of animals is inefficient and has been estimated to be about 10% in pigs. The chemical form of the zinc, and also other factors in the diet, markedly affect the efficiency of absorption. Low levels of zinc in the animal's feed tend to enhance the absorption of the ingested element. Zinc deficiency never occurs under practical conditions. An experiment has been described in which pasture was irrigated with water contaminated with ^{65}Zn . Zinc concentrations in grass were 440 times those of the water, and in milk and muscular tissues of cows eating the grass, 27 times those of the irrigation water. Normal zinc levels in milk of cattle vary from 1-6 mg per liter.

Manganese is also widespread in the animal body, and although it is not concentrated in any specific tissue, the highest concentrations are found in liver and kidney. Absorption by the gastro-intestinal tract is low and has been estimated at 4% in the rat. In rumen samples of sheep, only 5-10% of the manganese in the grass was found to be in soluble form, and this reduced availability may explain the low absorption. A large portion of the absorbed Mn is secreted in the faeces via the bile. Corn has an extremely low content of Mn. It is not known if this influences the absorption of the element. The secretion in milk is small and variable, from about 12-120 microgram per liter. After intravenous injection of ^{54}Mn , about 0,5% of the dose was recovered from milk, indicating that this route of secretion of Mn is unimportant.

5.3.2.3. Isotopes of iodine

In the period of nuclear fallout, the transfer of iodine from plants to animals has been studied under field conditions. Important information has become available but the influence of some parameters remains uncertain. For example, there is some doubt regarding the exact quantity of iodine deposited on and retained by the plant. Also, the transfer of iodine by the animal into milk is influenced by seasonal factors and variations in milk production, the effect of which is not known with certainty.

5.3.2.4. Plutonium

Intestinal absorption of Pu in mammals is very small but has been reported to be dose-dependent and to decrease with age. In pigs, resorption of orally administered Pu in soluble form was found to be 0,002%. Some studies have given indications that actinides may be absorbed differently by the animal organism when incorporated into plants. On the basis of these results, this route of intake of actinides needs further study. The transfer coefficient of Pu from plant to animal is estimated usually at 10^{-3} to 10^{-4} .

6. CONTROL OF THE TRANSFER OF RADIONUCLIDES AND ASSOCIATED POLLUTANTS

The best course to reduce the transfer of radionuclides to man would be the elimination of contaminated effluents. In accident situations, however, large amounts of radionuclides can escape. The ways of release are the same as during normal operation, namely the gaseous and liquid effluents, which are released to the aquatic and/or terrestrial ecosystems. The different pathways of the radionuclides in the environment are outlined in figure 1 (p. 185). This figure indicates the transition phases during which the transfer of radionuclides might be reduced. Apart of effective decontamination of surface- and subterranean water, the terrestrial ecosystem and treatment and/or storage of agricultural products are the most suitable places for control of the transfer. The pathway deposition on the crop → cattle → milk and meat → agricultural products → alimentary products → human diet is the most important pathway for short lived radionuclides as iodine-131. For longer lived radionuclides the pathway soil → vegetation → agricultural products

has to be included and for some radionuclides the pathway soil → resuspended aerosol → inhalation may be relatively important. The total radiation dose to man will depend on inhalation and ingestion. Although this radiation dose often can be computed only in a conservative way, i.e. a worst case analysis, this computation determines whether or not, and to what extent, protective measures have to be taken. Whenever the degree of contamination of the different steps in the pathway is accurately measured and if the main radionuclides involved are identified, the calculation of the radiation dose becomes more exact and more suitable measures can be taken. This emphasizes the advantages of *in situ* field measurements over laboratory measurements by avoiding the time consuming procedure of sampling, transport to the laboratory and analysis. The development of gamma-spectrometric techniques for field measurements will enable rapid measurement of contamination levels, accurate demarcation of contaminated areas and quick estimation of transfer processes in the ecosystem. Methods to reduce and possibly to eliminate the transfer of radionuclides to man can be divided into:

- a) Chemical ways to immobilize the radionuclides in soils. These measures also may result in reduced availabilities of the contaminants for plant uptake. Examples of such intervention are the application of complexing agents (e.g. uncharged ligands, mixed ligand chelates, alginates), organic materials (e.g. peat), synthetic or natural aluminosilicates.
- b) Measures to prevent resuspension of radionuclides deposited on the soil by using soil stabilizing chemicals, organic materials, etc.
- c) Mechanical ways to reduce the contamination by removal of contaminated crops and/or contaminated top soil. These practices may be combined with those of immobilization to stabilize the situation. Deep-ploughing which is traditionally advised seems less favourable.
- d) Decontamination of the rooted soil layer by enhanced leaching (eventually after chemical treatments to increase the mobility of the radiocontaminants). This solution only can be used for short lived radionuclides.

- e) Plant nutritional measures, e.g. application of CaCO_3 to reduce the transfer of strontium, use of adequate chemicals.
- f) Changes in agricultural practices by e.g. altering crop rotations (growing crops having lower transfer to the edible parts), growing crops to be treated according to the measures indicated sub 8, changing arable land into grassland (use of cattle as a filter during the transfer process to man).
- g) Administration of chemicals to farm animals to reduce the transfer to milk and meat; e.g. application of alginates, chelates, mixed ligand chelates, Prussian blue, vermiculite.
- h) Product treatment to reduce the contamination of agricultural products by e.g. the production and storage of milkpowder made from milk contaminated with iodine-131; production and storage of sugar from sugarbeets, of flour from cereals, and of starch from potatoes grown on contaminated land.
- i) Change of the distribution patterns of agricultural products to increase the dilution factor and to avoid local consumption of contaminated food. Assuming linear dose-effect relations, the radiation dose to the whole population remains the same, but the individual dose is reduced.
- j) Preparation of foodstuff, e.g. increased transfer of radionuclides from non-edible to edible parts by acid treatments.
- k) Control of thermal pollution by utilization of the heat for useful purposes. Apart of the direct beneficial effect, e.g. decrease of the dissipation of heat to the environment by using it in pisciculture, also synergistic effects, e.g. between increased environmental temperature and transfer of radionuclides to crops and water biota, will be avoided.

Of each of these methods, the list being far from exhaustive, the practicability has to be evaluated in relation to the extent of the contaminated area and in relation to the degree of contamination.

7. GENERAL OUTLINE OF THE PROGRAMME

The following topics should be retained for the future programme concerning the effects of contamination by radionuclides on terrestrial and surface-water ecosystems. Emphasis will be on effects which ultimately affect quality of human life and on their control by appropriate procedures.

- a) Definition of the main parameters which condition the distribution of specific radioactive substances is of interest in relation to the following aspects of this first topic. More information is needed on the exchange of ^{14}C and HTO between the atmosphere and the various compartments of the ecosystems considered here. This also applies to data on the atmospheric dispersion and deposition processes of long lived radionuclides in urban areas; these data are of particular interest with respect to an estimation of the possible interaction with pollutants from e.g. conventional power plants (see 3). As a source for cross-contamination, resuspension of radionuclides from the sea surface, silts and typical european land surfaces requires special attention for such elements as Np, Pu, Am, Cm and long lived fission products.
- b) Next to an improved knowledge on the distribution pattern of radionuclides in specific situations, realistic data on their transfer between various compartments of terrestrial and surface-water ecosystems have to be worked out.

With respect to the aquatic environment this mainly applies to two aspects. Particularly for the transuranium nuclides and long lived fission products more information is needed on the transfer to sediments. Also the uptake by aquatic species of specific radionuclides, such as technetium-99, americium-241 and curium-246, has not sufficiently been studied.

For the terrestrial environment, data are needed on the migration and retention mainly of transuranium nuclides and long-lived fission products in various types of rocks and soils of Community countries. These data, which better define the availability of such elements, are of interest to further studies on the transfer of radionuclides, deposited on the surface of agricultural land, in arable soil, to surface and ground water and after uptake in crops to animals. Particular attention should be paid to the transuranium radionuclides, members of the thorium and radium decay chains, as well as to tritium, carbon-14, sulphur-35, technetium-99, ruthenium-106 and iodine-129.

The way in which the systematic contamination of compartments of the agricultural food chain might be influenced by the incorporation of mainly such radionuclides as tritium and carbon-14 in biological materials of plants and animals under conditions of chronic contamination needs careful study.

Finally within this topic and in relation to the first one, our knowledge on the regional distribution and behaviour of long lived radionuclides (e.g. carbon-14, technetium-99 and iodine-129) should be increased with particular reference to a better definition of their exchange between the aquatic and terrestrial ecosystems and in general between different compartments of the environment.

- c) The next topic of the programme emphasizes investigations of possible synergistic effects of radionuclides and conventional pollutants released to the environment. It is obvious that within the scope of this programme mainly data on synergism in uptake of contaminants in important links of the food chains are of considerable interest.
- d) The final topic of the programme requires a thorough evaluation of methods to reduce the transfer of radiocontaminants to man.

8. CONCLUSIONS

Radionuclides which presently appear the most important are the transuranic elements (Pu, Am, Cm), ^3H , ^{14}C , ^{35}S , ^{85}Kr , ^{99}Tc , ^{106}Ru , ^{129}I , ^{131}I , some activation products (^{54}Mn , ^{60}Co), long lived fission products (^{90}Sr , ^{137}Cs) and the natural radioisotopes (radium, thorium and daughter products). The chemical toxicity of some of these nuclides (^{99}Tc) must also be considered.

The main environmental transfer processes requiring further investigations are:

- the atmospheric dispersion, deposition and resuspension processes in urban areas.
- resuspension of radionuclides from the sea surface, silts and typical European land surfaces.
- the transfer of radionuclides released to the aquatic environment and their possible remobilization from sediments.
- the uptake by aquatic species of long lived radionuclides.
- the migration and retention of radionuclides in a range of rocks and soil types typical of Community countries, particularly the transuranium nuclides and long lived fission products.

- the transfer of radionuclides deposited on agricultural land to water, plants and animals. The way in which the systematic contamination of animals might be influenced by the incorporation of radionuclides in biological materials and by conditions of chronic contamination needs special attention.
- the regional distribution and behaviour of long lived radionuclides with particular emphasis to their exchange between different sections of the environment.
- the influence of possible synergistic effects of radionuclides and conventional pollutants released to the environment with particular reference to the incorporation of radionuclides into food chains.
- measures to reduce the environmental transfer processes.

MARINE ENVIRONMENT

1. Significance of the subject

The study of radioactivity in the marine environment is now some 30 years old and a considerable volume of basic knowledge has been acquired in respect of the behaviour of radionuclides. In the case of the majority of artificial radionuclides likely to be deliberately introduced to this environment in the context of controlled waste disposal operations sufficient knowledge is now available in this respect to ensure that such introductions can be effected without undue radiological penalty.

However a detailed understanding of the mechanisms leading to the observed distributions, and consequent radiation regimes is still largely lacking and much further work needs to be prosecuted in order to ensure that all regulatory procedures are on as sound a scientific footing as possible; this is especially true in relation to the longer lived radionuclides and their significance for human radiation exposure over long periods of time (millenia). It is also true in relation to particular segments of the marine environment and perhaps especially so in relation to the deep-sea and its cost-effective use as a disposal environment.

There are number of significant changes that have occurred since 1974 that dictate important changes in direction of community research effort amongst which might be singled out the increasingly important need to assess collective dose and collective dose commitment over wider oceanographic areas and longer spans of time : the diminishing importance of assessing damage to marine resources following completion of the IAEA assessment of this problem and the views expressed in ICRP 26 : and confirmation of the assessment of potential human radiation exposure as the dominant requirements, thus ensuring an adequate protection of all compartments of the environment.

It should also be recognized that many of the data collected in existing radioactively labelled environments during investigations into dispersion and reconcentration of radioactivity by organic and inorganic

materials and by living organisms have a contribution to make to basic problems of marine ecology and oceanography. This is particularly true for such areas as circulation and mixing of water masses, chemistry and physico-chemistry of seawater and sediments, metabolism of marine organisms, marine ecology, and marine instrumentation. Moreover, radiation protection research has produced and will continue to produce much information useful in understanding the behaviour of other marine pollutants.

The nuclear industry releases radioactive material into the environment, and particularly into the water. It also releases non-radioactive chemicals and heat. These 3 factors may interact and such possibilities should be given due consideration.

2. Important sources of radioisotopes

The importance of radioisotopes as pollutants and possible health and environmental hazards depends on their nature, mode of release and the characteristics of the receiving environment.

2.1. Fuel reprocessing plants

In the context of human radiation protection the following general statements can be made :

- For β -emitters e.g. Ru, Cs and Ce, contamination of the food chain probably represent the limiting factor in the disposal operation because of the possibility of exposure of the internal organs of consumers, especially the gastro-intestinal tract (GIT)
- Contamination of beaches may set limits to the discharge of γ -emitters (Zr/Nb, Cs), due to external exposure. Likewise limits on beta emitters (such as Ce) may in some circumstances be set by contamination of fishing gear.
- Tritium occurs in large quantities particularly in the waste of fuel reprocessing plants. In view of its possible effects on genetic material it deserves further consideration.
- α -emitters such as Pu, Am, Cm and Np, which are present in waste from fuel reprocessing plants, also pose potential problems via the food chain (e.g. GIT irradiation). In later years, when higher burn-ups will be achieved, the importance of Am as a radioactive pollutant may increase.

- New reactor technologies could lead to new fuel reprocessing problems. These in turn could bring about an increased emphasis on some radioisotopes.

2.2. Reactors

When compared with the radiological protection problems posed by the operation of fuel reprocessing plants, those derived from reactors are of the same nature, but less important. They are usually local problems, very much depending on the type of reactor.

In addition to fission products which might be released as a result of fuel element failure, activation products are present in liquid effluents. Which of these activation products would predominate in the environment in a particular situation depends largely on the materials used in the construction of the reactor or in fuel element cladding, and the nature of the receiving environment.

2.3. Research and various technological activities

The composition of radioactive waste from research and technological activities involving radioisotopes varies so much from case to case that it is not possible to establish a general list of priorities.

As a rule, the small concentrations used will not present any special problems. Nevertheless, in defined circumstances and in local situations, where control has been inadequate they might present problems which deserve attention though they will be similar in principle to those posed under 2.1. and 2.2.

2.4. Accidents

Accidents to shore-based or island-based reactors would very predominantly result in atmospheric contamination. They could nevertheless involve some problems of marine contamination via deposition to the water surface or beaches and perhaps in the case of a rupture of the cooling circuit, release radioactivity directly into the sea.

More severe problems are likely to be associated with marine propulsion reactors than with power reactors. For an accident occurring to a propulsion reactor, it is difficult to predict the relative importance of the radionuclides that would be released. During the first week after a major accident it seems that iodine would be the principal service of exposure via the thyroid through contamination of food. As iodine

decays it would be followed in importance by other fission products such as cerium and ruthenium, and activation products. These also effect exposure via food, but the GI Tract would be critical in respect of beta emitters. Barium and lanthanum could become important beach contaminants due to external exposure from their gamma emitters. Accident modelling in a marine context deserves special attention. A data base partly exists for building predictive models, but it still needs improvement..

3. Behaviour and effects of radioactive and stable isotopes in relation to the marine environment

3.1. General

Since inland waters are already subject to considerable stress from industry and should so far as practicable be protected from pollution, an increasing number of industries, both conventional and nuclear, are being, or will be, sited near the coast. This increase in the number of coastal site may result in greater coastal pollution. An adequate understanding of the processes governing the distribution, dispersion and reconcentration of various waste products is therefore necessary in order to set and implement adequate controls to prevent pollution from radioactivity released directly into the sea or reaching it from the rivers.

3.2. Physical aspects

3.2.1. Sources of contamination will in most cases be near the coast, rather than in the open ocean or the deep sea, and shallow water will therefore continue to have more immediate importance than deeper sea areas as regards assessment of their suitability for the disposal of radioactive and non-radioactive wastes. Nevertheless, more attention than in the past should be given to the deep-sea as a receiving environment. Small scale (1-10 km) and medium scale (10-100 km) distribution patterns are now in general sufficiently understood for sensible control procedures. However, more data are required on larger-scale circulation (100-1000 km) in relation to longer lived isotopes in order to predict long range effects. Long-range low-level distribution surveys of specific radionuclides could provide a useful insight into these problems, as well as to basic oceanographic problems. However, data on deep-sea dispersion processes are also required for the conduct

of studies on the deep-sea disposal of wastes, especially those containing very long-lived isotopes.

3.2.2. Estuaries and adjacent shallow sea areas have unique features and present particular problems as a result of changes that occur in salinity and suspended sediment load at the freshwater-salt water interface. Whilst the distribution of radioactive materials can be broadly described by, e.g., following patterns in salinity, temperature and suspended matter, the processes involved and the mechanism by which they occur are not fully understood. The processes involved can also be studied by means of tracers - either deliberately introduced and followed for this purpose by experimental means, or by exploiting indicator materials in environments which have been labelled by radionuclides in effluent releases.

3.2.3. Existing knowledge of dispersion processes in the open sea is incomplete and in the deep-sea particularly scanty. The deep sea, being remote from human activity and from fishing grounds, would be expected to be more suitable than shallow waters for receiving waste. However before it can be fully assessed as a disposal environment particularly in the case of high level waste disposal, a much better understanding of vertical and horizontal dispersion processes is required, as well as of interaction between waste components and sediments.

At present, the convenient study of the deep sea as regards waste disposal and contamination is especially handicapped by instrumentation available at a reasonable cost. This is a problem of long-term investment which is posed on a scale broader than the Community alone, it requires wider international collaboration.

3.3. Geochemical aspects

3.3.1. A thorough understanding of the redistribution of radionuclides in the marine environment requires a much better marine geochemical background knowledge, particularly in the context of water-sediment interactions, including behaviour in sediments.

One particular difficulty in predicting the reaction kinetics of radioisotopes is due to the fact that they are present in very small chemical concentrations (10^{-9}M), whereas the whole approach to physico-chemistry has been founded on experimental data in the concentration range of $1\text{--}10^{-3}\text{M}$. The few data so far available in the 10^{-9} range show that extrapolations from the 10^{-3} range to

the 10^{-9} range, and even lower for actinides, are highly suspect. Predictions are further complicated by the complex chemical composition of seawater and sediments on the one hand and of the waste solutions on the other, especially with regard to the various physico-chemical states. Matrix-effects, particle size function, adsorption-desorption on surfaces, competition between ions, isotopic exchange and complex formation are some of the subjects which call for further investigation at these low concentrations.

3.3.2. Prediction of the distribution of radioisotopes may be facilitated by data on the distribution of stable isotopes of the same or chemically similar elements in seawater, sediments and organisms. In recent years increasing evidence has been obtained of the importance to be attributed to the physico-chemical states (e.g. valency states, solubility, colloidal nature, particle size) of elements. However, owing to the scanty knowledge of marine trace element chemistry in general and those elements which are directly relevant to radioactive contamination in particular predictions are still very difficult. The representative sampling of sea water presents serious problems, and in-situ, or at least "on-board" determinations, are very attractive in order to minimise variability and should be given priority in the development of new methods. There is a need for the development of seawater sampling methods and analytical procedures, suited for determination of low level concentrations of various radionuclides, and for simple sampling systems suited for collecting radionuclides from large volumes of seawater.

3.3.3. Liquid effluents are sometimes diluted in fresh water and may contain large quantities of complexing agents. When the waste solution mixes with sea water, the various constituents in both solutions interact, with the result that very often their physico-chemical states change considerably. Interactions of fresh- and sea-water and precipitation in these circumstances should be thoroughly understood before predictions, especially on a long-term basis, can be made.

3.3.4. In the context of the normal geochemical cycles, the ultimate fate of some radioisotopes will be sorption onto sediments. Also, sorption on sediments is for most radionuclides a factor which is permanently important in their shorter-term cycling. However,

present knowledge of the sorption capacity of the various types of marine sediments is limited and needs to be developed.

3.4. Biological aspects

3.4.1. The biological aspects of marine contamination have received a good deal of attention in the past, since the return of radioactivity to man through the food chain has been the critical factor in most waste disposal operations. In certain cases, fishermen and their families or persons employed in fish-processing industries have been considered as "critical groups" because of their high consumption of cheap and readily available marine products. However,, whenever the "optimization" concept has to be applied, it is necessary to assess collective dose.

In general, a definite trend towards a more rational and more reasonable exploitation of biological resources of the sea can be recognize and important steps have been taken in that direction. Any injudicious action which could reverse this trend should therefore be carefully avoided. The need to keep the disposal of radioactive waste in the marine environment under proper control has been recognized in certain provisions of the London, Paris, Helsinki and Barcelona Conventions, or in certain conventions refering to the maritime environment of the Community.

Organisms present in the marine environment disperse, reconcentrate or modify the chemical form of radioisotopes, and pass a fraction of them back to man via the food chain. Where a detailed understanding of the underlying processes is necessary, information would be required on distribution of organisms in space (including those living in sediments) and time, on their capacity to disperse and reconcentrate radioisotopes and stable elements, and on the transfer paths of radionuclides via the food chain to man.

3.4.2. The distribution of marine organisms in space and time has long been a subject of study, but even today quantitative investigations are still hindered by inadequate sampling techniques at many levels of the food chain and especially in relation to deep ocean areas. The distribution and migration of marine organisms and variations

in distribution with season and various stages of the life cycle represent a class of basic information required for some aspects of impact assessment.

Special attention should be paid to species which, even if they are of no direct commercial use, constitutes important links in the supporting food chain of commercially utilized species. In particular their proper use as pollution-indicators should be investigated.

Of particular importance in relation to deep-sea disposal may be the exploitation for human food of cephalopods.

- 3.4.3. Laboratory experiments on uptake and loss of radionuclides have long been handicapped by a lack of knowledge on how to culture and breed marine organisms under laboratory conditions. Much progress has been accomplished in this respect, but the representativity of the experimental system often remains a questionable. It remains true that more experiments in better conditions should be performed, at least for certain elements where more refined data are necessary.

The special importance of food chain as the major pathway for many radionuclides is now more widely appreciated, but there still remains a need for more experimentation on specific questions of physiology of certain elements such as transuranics (e.g. absorption of Pu in the G.I. tract). The design of such experiments has important consequences on deductions about uptake, turnover and loss. Investigation of this kind should be supplemented by observations in nature (in disposal areas) and by semi-controlled experiments in natural environments.

3.4.4. Radiation effects on marine organisms

- 3.4.4.1. In recent years several reviewers have indicated that doses of some 10 to 100 rad or dose rates of the order of 1 rad.d^{-1} are needed for the manifestation of a radiation effect in aquatic organisms*. Compared with the latter figure estimated dose rates

* "It can be concluded that 10^{-4} to $10^{-1} \text{ rad. h}^{-1}$ is the most important range of dose rates in which irradiation experiments with aquatic organisms are required, if they are to have some relevance to environmental problems" Technical Report 190 IAEA.

actually experienced by marine organisms are low, even in those environments which are contaminated with radioactive waste. Because of physiological or ecological masking, the consensus is that deleterious effects would not be detectable at dose rates presently experienced by natural populations. It is now felt that further experiments and observations similar to those of the past 25 years will no longer essentially add to the knowledge necessary to form a reliable judgement on possible effects of the present practice of radioactive waste disposal.

- 3.4.4.2. Due to the problem associated with the long-term storage of actinide-containing wastes, as well the increasing quantities of these isotopes in the nuclear fuel cycle, the possibility exists that their inventories within marine ecosystems could increase due to their release into the environment. As little experimental data are available concerning the effects that transuranic nuclides could have on marine biota, some more information should be at hand in order to determine conclusively the effect of alpha-emitting radionuclides on marine organisms.
- 3.4.4.3. As the absorbed dose rate is the universal measure of radioactivity and as the accuracy of dose-rate estimates could be improved, it seems worthwhile to carry out research to refine the dosimetric models in respect to a more realistic geometry of the organisms, distribution of radioactivity within tissues and relative biological effectiveness. As many variables as possible should be incorporated into dosimetric calculations.
- 3.4.5. As already mentioned earlier, nuclear industries release not only radioactivity, but also a whole series of chemicals and heated water. So far little is known about the combined effects of these various factors, but it can be assumed that interactions do exist. This is, in fact, also true for other so-called conventional pollutants such as oil, detergents, organic matter of sewage, industrial wastes, and pesticides. Increased water temperatures do not necessarily have deleterious consequences. It has already been shown that uses of warmer waters can be profitable in certain circumstances. In other cases, however, harmful effects on organisms have been recognized; these deserve further attention. Organisms at lower latitudes live close to the upper limit of their

heat resistance under normal conditions; this fact should not be neglected when selecting sites for power stations. It must be born in mind that synergistic relations or interactions between increase of water temperature and radionuclide uptake and accumulation may exist.

Some waters have long been burdened by sundry pollutants. The questions arise as to what degree this pollution may have acted as a selective force cahnging the gene frequencies in populations inhabiting the polluted areas, and to what extent a reduced genetic variability leads to a change in the capability to tolerate changing environmental conditions and stresses that might normally be expected, e.g. elevated radiation background in combination with extreme temperatures and salinities.

Some pilot studies could be done to find whether the experimental treatment of interactions and the application of stress studies to radiation research could be of practical relevance.

4. Some areas and topics of general importance

4.1. Intercalibration, advanced techniques

Past experience has shown that intercalibration and comparison of analytical measurement, and sampling (including sediment sampling) methods are of great importance for an efficient exploitation of data obtained by different research workers. Several international organisations have set up intercalibration programmes and panels which are to recommend reference (and not standard) methods. Still, much remains to be done in all fields of marine research.

Hence, the development and application of new techniques for the solution of marine contamination problems should be considered as important in future programmes. Special emphasis should be put on the development of in situ techniques. An important exemple is the experimental use of Pu237, which should be made more easily available, and the efficacy of its use should be improved through inter-group collaboration.

4.2. Improved models

As already mentioned, the problems of long term and large scale prediction will present a need for more elaborate models. Accident

evaluation and prediction of such effects deserve special attention. In the past, most marine radiocontamination work has been done in fall-out or in a controlled waste-disposal context. Accident-hazard evaluation calls for models which differ from those used for controlled release, and requires a general assessment of the types of situation which could arise.

There is a need to ensure a relevance and a proper relationship between modelling activities and research whether in the laboratory or the field. The two activities should follow parallel and interacting paths.

4.3. Turbulence, advection, mixing

More information is required on the role of turbulent mixing in shallow waters with small tidal movements. This is particularly the case for the Mediterranean sea, where also in summer a constant temperature layer (thermocline) is established and the mixing of surface effluents is limited to the upper compartment. The case of estuaries in the Mediterranean region also requires special consideration on account of the lack of relevant tidal movements.

4.4. Accidents

Any accident which might lead to emission of radioactivity or to modification of the behaviour of radionuclides in the environment, should be exploited fully as a source of information. This information should help to define intervention needs and methods aimed at restoring equilibrium conditions, and possibly at modifying or adapting radiation protection measures.

5. Conclusions

5.1. General

Present knowledge can be considered as adequate for overall routine control purposes based on the present safety standards and regulations. The increased use of fission energy in the future calls for the maintenance of an adequate degree of control procedures. Some problems need further attention in order to set up methods which are more economic and better adapted to these situations. Thus, in the long term, our ability to cope with future foreseeable or unexpected situations will be materially improved by a better understanding of the environmental

processes involved in marine radioactive contamination.

It will be much easier to arrive at a general acceptance of waste-disposal standards if the models on which the standards ultimately depend are developed and accepted by the scientific community as a whole in the countries concerned.

Future programmes should take account of the various characteristics of the seas surrounding the Community such as

- the Atlantic, the Channel, the North sea : medium salinity, significant water exchange and tidal mixing, medium temperature;
- the Baltic : low salinity, small exchange, weak tides, low temperature, stratification;
- the Mediterranean : high salinity, small exchange, very weak tides, higher temperature and stratification.

Available information differs both in quantity and in quality in these various zones.

Future programmes should take advantage of unique situations and competences presently existing in the Community, such as areas where waste-disposal operations are actually carried out, groups which have been faced with accident problems and procedures, and laboratories which have developed particular skills.

These situations and competences should become focal points for coordination and integration.

Better relations and co-ordination should be implemented between laboratories participating in the Community programme.

5.2. Subject areas of direct relevance to radioactive contamination problems.

5.2.1. Basic information

- collection of data on diffusion, advection, mixing and dispersion processes especially in actual contamination situations, by following radioisotope distribution;
- biogeochemical aspects, particularly of processes governing the rate of exchange at various interfaces : sediment-water, water-organisms, sediment-organisms, air-water, air-sediment (in estua-

ries);

- physico-chemical speciation of stable and radioactive isotopes in relation to their biological availability and interaction with sediments.

5.2.2. Levels assessment

- collection of better data on cycling of radionuclides and on biological half-lives (particularly relevant to accident situations);
- survey of long-range low-level distribution of specific radionuclides, especially in relation to the assessment of collective dose and collective dose commitment;
- improvement of dosimetric procedures and methods, in relation to the assessment of doses to marine organisms.

5.3. Techniques and methods of direct relevance to radioactive contamination problems

Progress is needed in the following techniques and methods

- intercalibration
- physical measurement techniques
- modelling and simulation
- sampling and analytical procedures

SHORT-TERM SOMATIC EFFECTS OF IONIZING RADIATION

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SHORT-TERM SOMATIC EFFECTS OF IONIZING RADIATION

1. Introduction

Fundamental and practical aspects of radiation protection have received major attention in the past decades. Nevertheless, there is a continuous need to increase the knowledge of cause, prevention and therapy of radiation injury. The radiation protection problems to be discussed here are concerned with the so-called early or short-term effects of radiation injury, i.e., injuries which are apparent shortly after irradiation and which (depending on dose, characteristics and distribution of the radiation) are amenable to proper evaluation and treatment. Consequently, a research programme in this field should cover : primary effects of radiation on biological material, early and continued evaluation of the extent and/or severity of the injury (diagnosis), treatment of localized and/or generalized injury. It is important to attain a maximal degree of harmonisation of the methods used for the evaluation and treatment of radiation injuries throughout the European Community. This may also require the establishment of courses to be given at the pre- and postgraduate level. Further, a comprehensive registry of radiation accidents, covering the evaluation, treatment, follow-up and other aspects of radiation injury, is urgently required.

2. Research on short-term somatic effects

The new programme should obviously take into account the know-how acquired in the past few years. For practical reasons, the topics can be subdivided into the following categories :

- a) the mechanism of radiation injury (primary effects on DNA),
- b) the evaluation of early somatic effects (including monitoring of damage and recovery),
- c) the treatment of radiation injury, covering damage caused by localized or by generalized irradiation (homogeneous or nonhomogeneous)

2.1. Primary effects

There can be no doubt that a better understanding of the primary mechanisms of radiation damage would be invaluable in controlling the consequences of irradiation on men. Actually, whatever biological system is irradiated, radiation damage is produced virtually at the time of exposure.

All subsequent biological effects are the consequence of chains of molecular events achieved within a fraction of a second after energy absorption. These fast events, corresponding to the sequential steps through which radiation energy is dissipated in living organisms are conventionally called "primary effects". They include : molecular excitation and ionization, free radical formation and, eventually, induction of permanent chemical alteration of macromolecules essential for normal cell function. The explanation of radiation injury in terms of primary effects is the radiation chemist's greatest challenge. However, that which only few years ago seemed an impossible task is now successfully investigated by means of recently developed techniques and dramatic advances have been achieved in three main fronts :

- a) a broad knowledge has been gained about the sites and structural properties of free radicals as reactive species mediating the pathway to stable chemical alterations;
- b) the latter have been analyzed in detail thus providing a clue to alterations of importance to biological malfunctions;
- c) biologically viable damage such as base alterations and strand breaks, has been well characterized in suitable model systems.

It can thus be concluded that, at this stage of rapidly increasing knowledge, fundamental radiation research at a molecular level should continue to receive high priority in the forthcoming programme. Details of the research programme in the field of primary effects are given under point 3.

- ### 2.2. The evaluation of early somatic effects has also been the subject of intensive research in the past decade. Various in vitro systems which permit an estimation of the extent and the dose level of a radiation injury have been developed. Those studies are intimately related to

investigations dealing with the regenerative capacity of various types of tissues ("rest function"). However, the available evaluation procedures are not yet optimal and not sufficiently standardized. Since early diagnosis and monitoring of rest functions of various cellular systems are of great importance for the choice of therapy after radiation injury, this line of research should be vigorously pursued.

As already indicated, radiation injury can be schematically divided into damage caused by localised versus generalized irradiation, whereby the degree and severity of the injury is obviously depending on the homogeneity of the radiation and its characteristics (RBE, LET, dose rate, fractionation, etc.). The main task in evaluating the injury will be the early and continued monitoring of the functional capacity of hemopoiesis, of the immune system and of various other cellular systems (epithelial tissue, connective tissue, central nervous system, etc.). All available methods to test the functional capacity and recovery of those cellular systems should be employed and new methods should be investigated. This part of the programme should further include detailed studies on :

- the physiology of stem cells derived from bone marrow or from peripheral blood and their migrating capacity between "compartments", further, early radiation damage to pluripotential cells and to more differentiated hemopoietic progenitor cells by chromosomal, biochemical and other indicator systems should be investigated;
- the differentiation and maturation of pluripotential stem cells into the erythroid, myeloid, megakaryocytic and lymphoid lines. A better understanding especially of lymphoid maturation and differentiation is important for so-called engineering of immune reactivity, a topic related to the immunological complications of bone marrow transplantation (see p.235). Hormonal and other regulatory mechanisms of differentiation, maturation and homeostasis, should also be investigated;
- the immune system. Topics to be covered include the short-term effects of various kinds of radiation on parts of or the entire lymphatic system, specific influences on the thymus, on the intestinal part of the immune system, on various subpopulations of lymphocytes and on their interactions in maintaining proper immunological defenses;

- the pathogenesis of localised radiation injury, with emphasis on the effects of radiation on the dermal epithelium, the underlying connective tissue and the cutaneous and subcutaneous vasculature.

All these studies should be carried out at various dose levels, intensity and quality of radiation, at single versus fractionated doses, after internal as well as external radiation. Of particular importance are studies on the effect of protracted irradiation since comparatively little is known about that subject. The investigations listed here should be performed in various animal models as well as in patients receiving X-ray doses for diagnostic or therapeutic purposes.

2.3. The management or treatment of short-term effects of radiation.

Radiation injury can be categorized according to various qualitative criteria such as internal versus external radiation, local versus generalized injury and the characteristics of the radiation or according to quantitative criteria such as dose level, dose rate and dose fractionation. Further, the degree of homogeneity of the irradiation is an important factor which must be taken into account. For practical purposes, however, the classification of injuries will be limited to two main categories, namely: local and generalized radiation injuries.

- 2.3.1. Local radiation injuries demand special attention in view of their frequency, the incomplete understanding of their pathogenesis and the unsolved problems connected with treatment. Depending on the great variety in the modalities of irradiation (external radiation versus absorption of radioactive material by ingestion, inhalation or wounds), local lesions may involve the skin, internal surfaces of the gastrointestinal tract, the respiratory tract and other organs or tissues. A particularly troublesome complication of local radiation injury is the damage to the omnipresent connective and vascular tissues which play an important role in healing processes. The comparatively high incidence of tumour occurrence in healing radiation burns also demands attention.

With regard to cutaneous radiation burns emphasis should be on : the healing process, particularly in relation to damage to the surrounding connective tissue and vasculature; conservative treatment

an reconstructive surgery; investigations of early changes which may cause delayed effects (excessive scar formation, oncogenic transformation, etc.); investigations of a possible role of the immune system in any of the consequences or complications of local radiation injury.

Most of these topics have been studied in the past decades and progress has been made in the understanding of the pathogenesis and results of the treatment of local injuries. However, since one is dealing with serious lesions which occur rather frequently, it is important to find entirely new approaches toward this type of research. In addition, the studies should be carried out for lesions induced by single, fractionated or protracted radiation given at various dose levels and intensity. Different animal models should be used and, if possible, lesions observed in patients receiving radiotherapy should also be investigated.

2.3.2. Generalized radiation injury. The blood forming system is the most radiosensitive of the vital tissues when the whole body or a large part of it has been exposed to ionizing radiation. In cases of irreversible damage to the blood forming tissues, the transplantation of hemopoietic stem cells is the only way to save a victim's life. This kind of therapy can be effective up to doses of about 1000 rad of homogeneous total body radiation (TBR). At higher doses, the damage to the intestinal epithelium or the central nervous system is usually such that fatal intestinal and cerebral syndromes will occur. Accidental radiation of the entire or large parts of the body is usually not homogeneous. Consequently, the therapy in such cases will have to be guided by careful clinical observation and by the continuous monitoring of the functional capacity and recovery of a number of the vital cell renewal systems of the organism.

The therapy of injuries to the hemopoietic system has been studied in previous programs and considerable progress has been made in understanding and treating the "bone marrow syndrome". Although proper supportive care and replacement therapy (stem cell transplantation) have gradually become accepted therapeutic approaches for human marrow aplasia (including that caused by radiation injury), this type of therapy is still wrought with complications, mostly of an immunological nature. The forthcoming research program should be primarily concerned with those specific

problems. The research areas to be considered are here subdivided into: supportive care, isolation and decontamination as well as general and immunological aspects of replacement therapy.

- Supportive care : Optimal supportive care will be required after any serious radiation injury. During the most critical period of the aplasia, transfusions of thrombocytes, granulocytes and/or monocytes will often be necessary. Therefore, the current methods of isolating and preserving those cell types should be improved and standardized. Likewise, the methods of monitoring and treating infections and disturbances of the fluid balance should be further studied and improved.
- Isolation and bacterial decontamination : in mice, bacterial decontamination abrogates the chronic type of Graft versus Host Disease (GVHD) after bone marrow transplantation. In primates (monkey and man), a beneficial effect of isolation and decontamination has been found when purified stem cells were used as inoculum; also recovery of immune reactivity seems to be accelerated in such "protected" recipients of hemopoietic stem cells, although the reasons for the beneficial effect are not yet known. Consequently, the subject requires further study and various laboratory techniques should be improved and standardized. In addition, special attention should be paid to the prevention and therapy of virological disorders. Victims of radiation injury are particularly susceptible to virus infections, regardless of whether they are treated conservatively or receive replacement therapy. Therefore, the application of new methods of antiviral treatment should be exhaustively investigated.
- General aspects of cellular replacement therapy: This includes several problems encountered when transplanting autologous or isogeneic hemopoietic stem cells (same genetic make-up of cell donor and recipient), or when allogeneic cells are given. The latter category can be subdivided into cases where marrow from related donors or from unrelated donors is used (1). Research topics to receive particular attention

(1) If the donor is a sibling identical for the major histocompatibility complex (MHC-identical), immunological complications are relatively infrequent and usually mild; unfortunately such donors are rarely available. If unrelated host/donor combinations are used, the sharing of tissue antigens (histocompatibility) plays a major role in the takeability of the graft and in determining the severity of the immunological complications.

include :

- * Defining the indications for cellular replacement therapy, particularly in cases where the radiation dose received has been non-homogeneous.
- * Determining the minimal dose of total body irradiation at which transplanted stem cells will "take".
- * Determining the minimal number of cells required for a take and for hemopoietic recovery (large numbers of allogeneic cells increase the chance of GvHD, except in autologous and isogeneic combinations).
- * Improving and standardizing the methods of stem cell separation from bone marrow and from peripheral blood (the acquisition of stem cells from the peripheral blood has logistic advantages, particularly if marrow banks are envisaged).
- * Improving and standardizing cellular cryopreservation and the monitoring of cell viability (e.g. storing of autologous marrow may be indicated for individuals in accident-prone areas).
- * Determining the micro-environmental factors which can affect cellular engraftment in a positive or negative fashion.

Some of the subjects listed here should be investigated in more than one animal species and, whenever possible, also in human subjects.

- Immunological aspects of cellular transplantation include the following:

- * Histocompatibility. The degree of histocompatibility between the stem cell or marrow donor and the recipient largely determines the severity of GvHD and other immunological complications after replacement therapy (takeability, restoration of the host's impaired immunological capacity, etc.). Since stem cells from MHC-identical siblings are rarely available (see footnote, p. 234), research should concentrate on the use of hemopoietic stem cells from unrelated individuals. In recent years, the possibilities of transplanting cells from unrelated individuals have improved. However, further research in host/donor matching is required; such preclinical histocompatibility research should be carried out in non-inbred rhesus monkeys and/or dogs.

- * The elimination of immunologically reactive cells from the inoculum. This can be achieved by various mechanical methods (gradient separation of stem cells, etc.), as well as by other means.
- * The induction of tolerance. Several new approaches to facilitate the induction of tolerance of the grafted cells toward the host tissues have been introduced (e.g. the exposure of the inoculum to antilymphocytic sera, etc.), but further research is required.
- * Monitoring and enhancement of immune reactivity in individuals having received cellular grafts after TBR. A major crippling factor in long-lived "chimeras" of any species is the slow and incomplete recovery of immune reactivity. Now that chronic GvHD can be mitigated and/or treated even when stem cells from unrelated donors have been transplanted, infections have become the most troublesome complication of replacement therapy. Thus it is important to improve and standardize the techniques of immunological monitoring, the symptomatic treatment of immune deficiencies and, hopefully, the enhancement of immune reactivity with immune-stimulants.

Most of the studies suggested here should be carried out in more than one animal model and, if possible, in human subjects. Small rodents can be used for fundamental work but dogs and monkeys should be used to test newly developed experimental methods prior to their clinical application.

3. Details on Primary Effects

3.1 Definition and significance of primary effects

When a living system is subjected to ionizing radiations, the damage is produced at the time of exposure. All subsequent biological effects are the consequence of chains of molecular events achieved within a fraction of a second after energy absorption. These fast events correspond to the sequential steps through which radiation energy is dissipated in living organisms : molecular excitations and ionizations, free radical formation and, eventually, induction of permanent chemical alterations of basic macromolecules. These initial steps in the overall path of radiation injury are conventionally called "primary effects". Primary effects are the molecular clues for an understanding of the mechanisms of radiation action and hence for possible control of their final effects in terms of active radiation protection or sensitization.

3.2 Introduction

The task of relating the biological manifestations of radiation damage, such as mutations or malignancies, to their underlying radiochemical causes, once seemed impossible for two reasons : the first was the absence or the scarcity of techniques capable of analyzing the short-lived primary processes; the second was the paucity of collaborative research between workers in the field of primary effects and workers in the field of somatic effects of radiations. For example, the Electron Spin Resonance technique (ESR) was discovered in 1945 and it became immediately clear that this technique could play a unique role in the study of free radicals. However, it was only in 1963, after years of successful applications of ESR to several physical and chemical problems, that the first free radical induced in DNA by ionizing radiations was unambiguously identified. Since that date and especially in the last few years, dramatic advances in the understanding of the primary effects of radiation occurred on three main fronts :

- a) The substantial improvement of the ESR technique, jointly with the discovery of multiple magnetic resonance techniques (ENDOR, Triple Resonance), permitted a broad knowledge to be gained of the sites and properties of most radiation-induced free radicals in DNA.

- b) The very sensitive analytical methods of modern chemistry have been used to identify stable radiation products in DNA and to infer from these products the mechanisms of their formation.
- c) The involvement of various radiation products in the induction of biological damage, such as point mutations and strand breaks, has been demonstrated in biologically active systems.

In spite of the definite progress in the above individual fields, the connection between the different disciplines remains insufficient. One is led to conclude that significant advances in this multidisciplinary field can be expected only from a highly coordinated, coherent research, conducted by physicists, chemists and biologists frequently meeting each other and sharing knowledge and techniques with a view to elucidate the whole mechanism of radiation effects, from the initial deposition of energy to its final biological consequences.

The following is a detailed description of the different topics which will be investigated in the course of the next five-years programme. The subdivision into four distinct parts, two main research areas and two interfaces, is maintained for the sake of clarity, but constant priority will be given to the collation of experimental data into a coherent mechanism.

3.3 Priority projects

3.3.1. Structures and reaction pathways of free radicals induced in DNA and related compounds.

A large specific portion of the biological damage induced by ionizing radiations is due to the formation of free radicals that react secondarily to bring about permanent lesions to DNA. The reasons for studying DNA-located free radicals are twofold : firstly because they represent the earliest radiation induced injury which can be extensively analyzed by means of well developed experimental techniques and secondly because, at this early stage, the sequence of events which would normally lead to radiation damage can still be interrupted or diverted towards less

vital targets by the interfering action of suitable additives. Research activity in this sector will therefore include studies of free radical structures as well as of the conversion reactions transforming primary radicals into secondary radicals and, finally, into non paramagnetic products.

3.3.1.1. Determination of structural parameters

The most suitable systems for obtaining maximum information on the structural parameters of radical species are single crystals. However, since a given crystal structure is not always obtainable or compatible with the problem to be studied, the use of randomly oriented systems sometimes becomes necessary. Thus, in order to provide the necessary link between the crystalline and the amorphous state, the single crystal data will systematically be used to provide accurate simulation of the corresponding "powder spectra".

3.3.1.2. Mechanisms of free radical conversion. Quantitative aspects.

Whatever the system used, priority will be given to investigations aiming at resolving, qualitatively and quantitatively, the radical reaction pathways. The experimental approach may be summarized as follows. Irradiation at very low temperatures (77K or 4K if necessary) will often give rise to the trapping of primary radical species. Then a stepwise annealing of the sample will allow these primary species to undergo free radical reactions involving the formation of secondary radicals. The overall process will thus appear as a complex sequence of radical gain and loss as a function of temperature. Identification of the different radicals present at each annealing step, and estimation of their respective yields will finally reveal the single radical reaction pathways and the temperature dependence of their respective yields.

3.3.1.3. The role of water in the mechanism of free radical induction and conversion.

Particular emphasis will be given to studies on water containing systems. Four types of environments are considered : hydrated single crystals, frozen aqueous solutions, glasses and fluid aqueous solutions. Although none of these systems is entirely

representative of the "living state", each one can successfully be used to elucidate one particular aspect of the problem. The aim common to all these approaches will be to probe the role of intracellular water in the radiolysis of DNA under *in vivo* conditions; in particular to probe the type and the extent of the DNA damage resulting either from the direct effects of the radiation, or proceeding via chemical attack of the diffusible free radicals formed in the radiolysis of water. It must be stressed that the choice of the additives (see point 1.5.) which are capable of interfering with the normal evolution of radiation damage, depends entirely upon the answer to this important and still unresolved problem.

3.3.1.4. Search for "reference systems" open to coherent investigation by different laboratories and by different techniques.

The systems' complexity will be increased; in particular, priority will be given to work with mono-, di- and polynucleotides, various forms of DNA, DNA + protein complexes and, possibly, some simple forms of living structures. The ultimate purpose will be to find one or several systems suitable for study, concurrently, by means of physical, chemical and biological techniques, after irradiation under the same experimental conditions. The biologically active ϕ X 174 DNA, irradiated in frozen solution or in a glass, investigated by ESR and, after thawing, by the appropriate chemical and biological techniques, is suggested here as a possible candidate.

3.3.1.5. Effect of additives on the nature and the yield of DNA-located free radicals.

Chemicals are known which interfere with the energy degradation pathways in irradiated organisms. Such interference may result in altered radical structures as well as in a reduction or enhancement of the total radical yield. Both modes of action furnish the possibility of control of the final radiation effects. In order to probe the previously resolved radical pathways and to interfere selectively with one or other branch, two classes of additives will be used:

- a) Additives possessing particularly high reaction rates with the water radicals : these substances do not need to be bound to DNA to be effective, but they need to be homogeneously dissolved in the water-rich regions.

- b) Additives capable of forming complexes with DNA. Their effects will be investigated in phase separated systems like frozen solutions or, in the dry state, after freeze-drying.

For both classes of additives, the possible bonus of a synergistic effect when a group of additives is used simultaneously, will also be taken into consideration. Such a "free radical approach" is obviously exploratory. Once a substance has been shown to display a marked effect on some free radical pathway, chemical laboratories will confirm the existence of a similar effect on the quality and the yield of the radiation products formed (see point 2) and, finally, biological laboratories will take over to decide whether or not the substance in question is an effective radiation modifier and to establish its toxicity.

3.3.2. Chemical characterization of radiation products in DNA and related compounds.

On a temporal scale, the end of the free radical stage is followed by a "chemical stage", encompassing the complex chain of chemical reactions among non paramagnetic products leading to the formation of permanent alterations in the DNA chain. The study of this chemical stage is crucial for an understanding of the molecular bases of the radiation induced biological malfunctions. Research activity in this sector will include investigations of two main classes of DNA lesions : release or degradation of nucleobases, and sugar-phosphate backbone breakage.

3.3.2.1. Base degradation in DNA constituents.

The study of the radiation products formed in the constituents of DNA irradiated separately is close to being understood for thymine derivatives. Similar studies will therefore be performed on adenine, guanine and cytosine derivatives.

3.3.2.2. Base degradation in DNA under in vitro conditions.

The above studies will help to furnish the necessary knowledge for the elucidation of the degradative processes taking place in DNA under different experimental conditions. The following points will be investigated:

- a) Whether base degradation occurs at random or, more specifically, at some particular bases.
- b) Qualitative and quantitative characterization of the different radiation products formed in the bases, will permit an analysis of the possible effects of various environmental factors, such as anoxic or oxic conditions, the pH, the DNA concentration and the physical state of the various matrices approaching the in vivo conditions.
- c) The existence of a possible dose-effect relationship on the relative destruction rates of bases and sugars will be investigated in greater detail. Preliminary studies have in fact indicated a preferential degradation of the deoxyribose moieties at very low irradiation doses.

3.3.2.3. Base degradation in DNA under in vivo conditions.

The problems for revealing the radiolysis products of DNA under in vivo conditions are thought to be qualitatively the same as those, described in the preceding section, concerned with irradiation of DNA under in vitro conditions. However, due to the small amount of DNA involved in a typical in vivo experiment, the present techniques of detection are not sufficiently sensitive. Progress in this field will directly proceed from future advances in chemical analysis technology.

3.3.2.4. Specific base degradation in di- and oligonucleotides. Consequences on replication.

Because of the random sequence of bases in DNA, additional and more precise information can be obtained from synthetic di- and oligonucleotides. The first step will therefore be the synthesis of oligonucleotides of given sequences, or of oligonucleotides carrying a known molecular alteration on a given base in the sequence. These substrates will then open up the possibility of performing crucial experiments on the action of enzymes involved in damage recognition and in the replication of the altered bases.

3.3.2.5. Degradation of the sugar-phosphate backbone *in vitro* and *in vivo*.

Previous studies on the free radical induced alterations of carbohydrates and phosphoric acid esters have revealed a large number of reactions which, in part, have been found to occur also in DNA *in vitro*. Where only qualitative results are as yet available, attempts will be made to obtain quantitative data. In these studies, emphasis will be made on lowering the substantially applied dose. This will cause considerable experimental difficulties and the sensitivity of the analytical techniques will have to be improved. Lesions at the sugar moiety which have been studied sufficiently in *in vitro* systems will be investigated *in vivo*. Once again a prerequisite is the development of very sensitive analytical techniques. Isolated cell nuclei or bacteria will be the first systems to be investigated.

3.3.2.6. The oxygen effect. The radiation chemistry of peroxy radicals.

The radiation sensitivity of a living cell is considerably enhanced when it is well oxygenated. This important phenomenon, the "oxygen effect", is probably mediated by the formation of peroxy radicals, issued from the addition of molecular oxygen to the primary radicals. The present knowledge of the chemistry of peroxy radicals in DNA and DNA constituents is still in its infancy. The clarification of the principal reaction pathways transforming the peroxy radicals into final products will be a major research objective in the next five years.

3.3.3. Studies at the interface between free radicals and radiation products.

The fact that most radical species are converted into permanently altered products is irrefutable. However, besides such a global relationship, no ordered relationship between the different elements of these two classes have been so far discerned. There is a sharp discontinuity in knowledge when radiation damage leaves the paramagnetic "space" of free radicals (passing beyond the vision of physicists and ESR spectrometers) to emerge into the diamagnetic space of chemically stable products (falling into the domain of analytical radiation chemistry.). Nevertheless, there are

strong reasons for believing that an elucidation of at least a significant portion of this critical interface will not present major difficulties. The following working plan shows how imperative is an interdisciplinary approach for such interface studies.

3.3.3.1. The one radical case.

Preliminary ESR studies will reveal the systems and the conditions favorable to the selective formation of only one radical species. Then collaborative experiments will be performed by ESR workers and analytical chemists : the former to identify the radical , the latter to characterize the product(s) formed after deactivation of the radical phase. Maximum reliability will be obtained if the above experiments are performed on the same irradiated sample (frozen or glassy samples, prior and after thawing).

3.3.3.2. The multi-radical case.

The results obtained from the experiments described above will definitely be confirmed and enlarged upon by similar experiments involving more than one type of radical. Again ESR workers will first find conditions leading to large changes in the relative yield of each radical. The use of specific radical scavengers is here suggested as an example. After each ESR experiment, quantitative analysis of the radiation products present in the different samples, will eventually disclose the ordered relationships between free radicals and chemically stable radiation products.

3.3.4. Studies at the interface between radiation products and biological damage.

Although the study of the biological malfunctions induced in irradiated organisms at a cellular, organ and whole body level is not within the scope of this part of the present programme, research activities in the sector of Primary Effects include the relation of the early physico-chemical events to the appearance of the first detectable biological effects. As for the preceding interface, an elucidation of the present "biochemical" interface is rendered possible by means of cross-fertilization experiments performed on the same material by different methods

and from different viewpoints. Work in this field can be done with biologically active DNAs isolated from certain bacteriophages. The following working plan details and marks the limits of the studies which will be performed at this interface.

3.3.4.1. Chemical nature of biologically inactivating damage.

a) Base damage and inactivation.

Although some progress has been made recently in disclosing the chemical nature of most damaged thymine residues in single-stranded DNA and its contribution to lethality, almost nothing is yet known about the contribution to inactivation of other damaged bases in double-stranded DNA. With some further developments of the available methods, this problem will be tackled.

b) Break damage and inactivation.

Both in single- and double-stranded bacteriophage DNA, alkali-labile latent breaks are found after irradiation. The chemical structure of these potential breaks, which proved to be lethal in both types of DNA, will be characterised in more detail, in particular in the double stranded DNA, because these sites might contribute to the lethal effects of radiation at the cellular level. Experiments will be carried out to make clear the quantitative conversion kinetics of well defined alkali-labile sites into actual strand breaks. Also the effects of a cellular environment on this type of radiation-induced damage in bacteriophage DNA will be studied.

3.3.4.2. Effects of additives on inactivation.

The protecting or the sensitizing effects of several substances, previously screened by ESR and radiation chemical trials, will be tested with respect to inactivation of biologically active DNA. Also the use of supercircular DNA and its radiation-induced conversion into circular or linear DNA can help to estimate the effect of such additives. In both cases, the quantitative aspects of the biological phenomena in study will be related to the quantitative aspects of the earlier physicochemical steps : free radical yields and G-values of the radiation products formed.

LATE SOMATIC EFFECTS OF IONIZING RADIATION

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LATE SOMATIC EFFECTS OF IONIZING RADIATION

1. Introduction

Two types of harmful effect may be induced in the irradiated individual, and may become manifest only at long periods of time after the exposure to radiation which causes them. In one type, classed as stochastic effects, the frequency with which the effect occurs depends typically upon the size of radiation dose, but the severity of the effects which occur does not in general depend upon the dose. The induction of malignant disease constitutes the most important example of such stochastic effects, in which the severity of any cancers or leukaemia which occur is independent of exposure to which it is attributable. However such effects are induced at a frequency which depends upon the dose received, and they may be induced at a low frequency even at the lowest doses.

In the other type, of so called non-stochastic effects, no significant harms is ordinarily detectable unless a substantial "threshold" dose has been exceeded, but the severity of the effect which is then produced may vary with the size of the dose which produced it. The induction of cataract or of reduced fertility, and the impairment of organ function of bloodsupply represent changes of this type, at least as regards changes of a degree causing impairment of normal function or activity, and such changes also may only become evident at long periods of time after radiation exposure.

Among the various sources of man made radiation, the exposures due to medical procedures represent the most important part. It is of the same order of magnitude as the natural exposures and shows a tendency to increase with time.

This situation deserves therefore a special attention in the frame of radiation protection. This is the reason why a separate chapter has been devoted to this question which is relevant to the late somatic effects of ionizing radiation.

The actinides and specially plutonium are the most toxic of the elements of the nuclear fuel cycle. This is due essentially to their emitting alpha particles of high LET and their long half life. This high toxicity justifies a special research effort. It has therefore been considered appropriate to add a chapter devoted to this important problem.

Tritium does not seem to be specially toxic. But the development of energy production by nuclear fusion will increase tremendously the amount of this isotope to be handled and it is of great importance to be sure that it is not more toxic than one thinks. A special study of this problem has been performed. It constitutes the third addendum to the section on the late somatic effects of ionizing radiation.

2. Induction of stochastic effects of radiation

2.1. Human studies

Malignant changes induced by radiation are of particular importance in regard to radiation protection procedures, since the possibility of their induction even at the low doses received during occupational exposure make it essential to estimate the frequency with which such changes may occur at low dose, so that an appropriate degree of safety can be ensured in working practice. The Commission therefore emphasizes the continuing need for two types of study.

Firstly, opportunity should be taken for assessing the frequency with which different types of malignancy occur in excess of normal expectation in groups of people who have been irradiated - for medical or other

reasons - at known dose levels, and have been or can be followed up comprehensively for the long periods of time - ideally of several decades - during which further radiation induced tumours may become detectible. This type of epidemiological study is valuable if it yields numerical estimates of the frequency with which malignant disease is induced in man, and in particular in different organs or tissues in man, by radiation at defined dose levels, since the frequency of such induction in human tissues cannot be inferred directly from the corresponding frequency in tissues of different animal species.

Although a substantial amount of quantitative information has been obtained by such surveys, including estimates of the risk of induction of malignant tumours in a number of organs or tissues, these estimates are often very imprecise and sometimes subject to uncertainties resulting from inadequacy of dosimetry, length or efficiency of follow up, or comparability of the control series with which they are compared. Moreover, information is commonly very incomplete on the influence of sex or of the age at the time of exposure, particularly at young ages, the mortality of radiation-induced tumours, or the way in which the latent interval between irradiation and detection of tumours varies with dose or with other factors. In addition, the influence of the quality of the radiation (LET) in inducing tumours is not established for any dose level or the variation of this influence (RBE) with dose; and the form of dose effect relationship for induction of human malignancies is known only very approximately in a few instances. Further studies giving reliable information on these subjects are clearly needed.

Some of the evidence on the carcinogenic risk of radiation in man has been obtained by study of groups of patients who have needed to receive repeated or extensive diagnostic radiological investigations. It is likely that the study of other groups of patients, examined in this way in the past, would yield valuable information if full records were obtainable - for example of the frequency of deaths from malignant disease.

Important information has also been obtained from the subsequent development of malignancies in patients who had received radiotherapy, particularly in treatment of non malignant disease of the spine, the breast or the uterus, at moderate dosage (of the order of a few gray). These data have been derived from study of patients treated in most cases by external radiation but in some cases following therapy by internal irradiation from administered radionuclides. Further studies of both types would be valuable if they were likely to yield additional risk estimates for cancer induction in particular organs, and if control data were obtained of the cancer incidence in patients with the same disease but who had not been treated by radiation. Information of this type would be of value also in giving guidance on the safety or otherwise of such forms of therapy for non-malignant disease. Similar studies on the effects of radiotherapy for malignant disease, whether given alone or in combination with chemotherapy, could also assist in defining the possible after effects of such treatments and the appropriate forms of such treatments to minimise the frequency of harmful late effects of this type. In particular, such studies may throw light on the possible synergisms between radiation and chemical agents, or a greater sensitivity to radiation carcinogenesis of the tissues in certain diseases.

Information of this type is, however, ordinarily obtainable only following radiation exposures that are considerably greater than those experienced occupationally. This is because the malignant changes induced by radiation are normally similar in character to those occurring in the absence of such radiation exposure. Any excess tumour incidence is therefore detectable only by statistical comparisons, and a small excess caused by exposure to low doses is likely only to be detected in very large and prolonged surveys.

2.2 Animal studies

There is consequently an evident need for fundamental experimental studies of the nature of cancer induction, and of the frequency with which malignant changes are likely to be induced especially by low doses. Such information can form the basis on which valid inferences can be made on the frequency of malignant change to be expected following the even lower doses involved

in occupational or other exposure to radiation.

In addition to the need to examine dose effect relationships at low doses studies on the comparison of high and low LET radiation, of radiation having different RBE and of dose protraction should be carried out with regard of tumour induction. Microdosimetric studies will be of great importance to evaluating effects in the low dose region.

Concerning studies after incorporation of radionuclides the following parameters should be taken into account :

- uptake (by ingestion or inhalation) radiation quality, half life,
- organ distribution, affinity to particular tissues, and inhomogeneity of deposition,
- metabolism and excretion
- studies on the benefit or possible harm of chelating agents.

For all those studies experimental models must be relevant both for fundamental research and for human malignancies. This involves an appropriate choice of animals (species, strain, virus susceptibility) and in vitro models, which are relevant to the particular end point under investigation. Special emphasis should be placed on the development of experimental models which include the variation of endogenous and exogenous factors which in part are likely to act as promoters in the carcinogenic process. These include age, sex, hormones, viruses, the immune system and local tissue reactions as endogenous and some aspects of cocarcinogenesis and synergistic effects as exogenous factors.

In animal experiments in addition to a study of the analysis of end points like the appearance of tumours, the exact identification of the cells at risk and more studies on the early and intermediate sequence of events during carcinogenesis are certainly needed. This will necessitate the development of new methods (including biochemical and immunological markers) for the early detection of the relevant effects, with special emphasis on pre- or early malignant changes

Furthermore the link between mutagenic and carcinogenic effects should be elucidated.

In order to improve the validity of long term studies, standardization of animal experiments would help to compare and, whenever possible, allow pooling of the results of different laboratories; this postulates a standardization of tumour nomenclature and quantification of morphological end points.

3. Induction of non-stochastic effects

In determining the procedures and the dose limits appropriate in radiation protection, it is important to know the types of non-stochastic effect which may be induced by radiation in man, the severity of the various such effects, and the dose level at which they are liable to be induced. It is particularly important to have information on those effects which might be induced by annual doses (of a few tenths of a sievert) continued over many years or decades.

This practical requirement applies particularly for those tissues or organs in which the rate of cancer induction per unit absorbed dose is likely to be low, since for these tissues the annual dose limit is less likely to be determined by the possible induction of malignancies than by that of harmful non-stochastic changes. Tissues of importance in this way are therefore those of bone which are estimated to have a low induction rate for cancer, and of skin and thyroid with a low rate for fatal cancer. For these tissues in particular, it is necessary to ascertain the non-stochastic effects which may occur, the severity of these effects, and the accumulated dose at which they may arise, so that the annual dose limit can be set for these tissues at such a level that the occurrence of any such harmful effects may be prevented, even after a natural or a working lifetime of exposure at the relevant dose limit.

There are some data for man, and many data for animals, on the radiation exposure, delivered as a single dose, which may cause non-stochastic effects. Some information is available also on the rather higher level of dose which is needed to cause such effect when the dose is delivered in fractions or continuously over a period of time - e.g. of a year or two in animals - rather than as a single exposure.

Much less information is available on the total accumulated dose, delivered over a substantial proportion of a human or an animal's lifetime, which would cause the same effects as are produced by the single dose. If the lifetime accumulated dose had a similar ratio to the single dose in several different animal species or for various different non-stochastic effects, it would give

some guidance on the lifetime dose in man which might cause such effects, relative to the single doses in man which are found to cause these effects.

Guidance on these questions needs therefore to be obtained from a review both of effects caused in man and on those induced in animals experimentally. In man it is important to survey the dose above which various non-stochastic effects are observed, particularly in the course of radiotherapy at which the appropriate dose levels are reached, but including where possible the effects of radiation at high LET, and those of treatment with radionuclides where relevant.

Experimental studies in animals will be valuable, as already stated, in examining the way in which prolongation of time during which a dose is given affects the size of total dose required to produce non-stochastic effects of different types. They will also be of importance in examining the way in which such effects are caused at the cellular or tissue level, since this study of their pathogenesis is likely to throw light on the importance of body mechanisms in their repair or of synergistic effects of other agents in their development. In addition, such studies of their mechanism of development should assist in defining the endpoints in their evolution which are of practical importance in causing limitation of health or activity, or of the ability of an organ to maintain an adequate functional capacity under normal conditions, or under conditions of stress when its functional reserves are involved. In this connection, it is necessary to assess the nature of any differences between the reactions of normal and diseased tissues to radiation, and the various established animal models of disease are likely to be of use. In many cases it is to be expected that the absorbed doses which give rise to malignant (stochastic) changes in a tissue will also have caused or initiated non-stochastic changes. Any interactions between the development of these two types of effect, or the influence of non-stochastic changes on the frequency with which cancers are induced and develop within a tissue, might be important in certain tissues or for certain types of radiation induced malignancy. The examination of the early phase in development of late non-stochastic effects could also prove important in allowing an assessment of the probability that such late effects were likely to occur.

The effects of radiation in inducing developmental defects in the developing embryo or foetus also require further study, both in regard to the frequency with which such effects are induced at various dose levels and at various stages in development, and also to establish which such effects are of a non-stochastic character and are induced only if a certain threshold dose is exceeded, or which may be induced even at the lowest doses, but with increasing frequency with increasing dose. It is, for example, important to establish whether, or to what extent, the mechanisms of inactivation, recovery or repair of adult somatic cells apply to embryonic cells, and the circumstances in which damage to single cells of the embryo results in major failures in development of the foetus. Few reliable estimates can be made of the frequency with which different types of developmental defect are induced in man by radiation, although enough is known to indicate the types of defect - most commonly of the nervous system - which are most likely to be induced. It will be important therefore to make studies on those animal species in which the same type of defect are most commonly induced, so that a suitable "model" can be used in examining the effect of radiation at different dose level, different LET, and delivered at different stages in development. Such studies should be of importance in estimating quantitatively the level of safety or of hazards involved in any radiation exposures occurring during pregnancy.

4. Radiation Exposure in Medical Diagnostic Procedures

4.1 Introduction

The use of X-rays in medicine is the largest factor in human man-made radiological exposure. A relationship exists between X-ray exposure and the appearance of genetic and so called late effects (malignant neoplasms). The exact relationship is, at least in the case of small doses, a matter of controversy. Knowledge concerning this point is based mainly on relatively high X-ray exposures (accidents, therapy).

X-ray should not be used in medicine without weighing their advantages against their risks. Such an assessment can be made only, when the risk can be calculated simply and with sufficient accuracy in relation to the dose level.

A prerequisite for determining the risk is knowledge of

- a) the extent of X-ray exposure of the individual and the whole population;
- b) the occurrence of malignant neoplasms, including leukemia, due to the routine exposure in X-ray diagnosis.

4.2. Exposure during a single X-ray diagnostic process and exposure of the whole population.

4.2.1. X-ray exposure of the individual

In the European Community, papers are constantly being published concerning the X-ray exposure of patients in individual radiological processes. Apart from the fact that in many cases the measured values referred to are too optimistic in comparison with the daily routine doses, even comparable radiodiagnostic examinations produce exposure values which vary widely. One reason for this might lie in the different procedures used for determining the organ dose, which yield results that in practice are not comparable. The different techniques (direct measurement on or in the organ, calculation of the organ dose from measured surface doses, or calculation of the

organ dose by means of instrument parameters (Monte Carlo method) cannot be solely held responsible. One also has to compare the different procedures step by step and then estimate the magnitude of the errors made.

It thus seems necessary to compile a catalogue for the European Community showing for each country the daily organ doses in respect of certain examinations (X-ray, fluoroscopy, therapy). The scatter must be stated as a function of the instrument parameters (voltage, current, combination of foils, screen, development conditions, etc.) and of the conditions prevailing in the X-ray examination (number of photographs at each examination, fluoroscopy time, etc.).

4.2.2. The mean population dose for each individual type of examination

From the points of view of X-ray protection, of evaluating the contribution of the individual methods to the whole population dose and of epidemiological studies, the mean population doses for the individual types of examinations are of considerable value. For this purpose it would appear necessary to produce another catalogue, which shows the number of radiodiagnostic methods in relation to the age and sex of the persons examined, to the type of examination, to the body region examined, to the film surface used and to the fluoroscopy time.

Such a digest of this type of the statistical material, which may already be available in some of the European Community countries, might give rise to some interesting findings (necessity of examinations, dose reduction, etc.).

This catalogue can be used to calculate the mean population dose, taking into account the individual doses and population size.

4.3 Epidemiological studies

For the assessment of the radiological risks, it is necessary to know, besides the organ doses, other values that enable conclusions to be drawn as to the possible consequences of a given X-ray burden (X-ray risk factors).

Extensive studies have already shown that in small additional radiological exposures, as is the case with most routine X-ray examinations, it is very difficult to establish a significant relation between X-ray exposure and health-damaging effects. One must therefore, try, in examinations involving a relative high X-ray exposure, to establish a relation between X-ray exposure and genetic or somatic X-ray effects. Population groups can be considered target groups if they underwent : mammography, examination of pneumothorax, or pregnancy examinations or if they include workers in nuclear power stations.

Other examinations which involve relatively high doses to the gonad or bone marrow are :

- high gonad doses :
pelvis, pyelography, femur, hips, lumbar, spine, stomach,
colon, urography, abdomen;
- high bone marrow doses :
stomach, pyelography, colon, lumbar, spine, lungs, heart.

The results of these epidemiological studies will form the basis for a risk-benefit analysis.

4.4. Conclusion

When all the results are available, consideration can be given to providing physician with a booklet from which he can obtain details of organ doses and risks for an examination in the light of the conditions prevailing in the special examination. Possibly one could then suggest doses-reduction, alternative methods for special cases with a minimum of exposure and risk. It is not satisfactory merely to define the type and extent of a risk : every possible way of reducing X-ray exposure must be tried. One of these ways might consist in securing constancy of quality and performing a quality check on the X-ray machines.

5. Toxicology of Plutonium

It should first be noted that with longer burn-up times of irradiated fuel americium and curium are now being produced in increasing quantities and therefore plutonium should not be studied in isolation. Furthermore the consideration of alternative fuel cycles would also require a knowledge of the biological consequences of exposure to other actinides, including ^{232}U , ^{233}U , ^{228}Th , ^{232}Th , ^{231}Pa and ^{237}Np .

5.1. Dosimetry

In the most recent recommendations of the International Commission on Radiological Protection (ICRP Publication 26, 1977), a new system of dose calculation has been adopted for internally deposited radionuclides which departs from the "critical organ" concept. The Commission now recommends a procedure which takes account of the total risk attributable to the exposure of all tissues irradiated.

For persons exposed to plutonium there are a number of tissues potentially at risk : the lungs, the lymph nodes draining the lungs, the liver, the bone marrow, the gastrointestinal tract and the gonads. For dose calculations for the liver and gonads it is adequate to assume that plutonium is uniformly distributed throughout them. There are a number of difficulties associated with dose calculation for the other tissues and on which more work is required in order to provide a better basis for calculating realistic Annual Limits of Intake (ALI's).

5.1.1. The bone and bone marrow

There are two sensitive tissues in the skeleton, the bone marrow and the osteoprogenitor cells that are considered to lie with $10\text{ }\mu\text{m}$ of the bone surface. At present it is assumed that plutonium is retained on the surface of the bone and is lost with a half-time of 100 years. Recent studies in man and animals have shown that processes of bone growth and removal can result in the burial of a fraction of the plutonium deposited in the skeleton, whilst another fraction is accumulated by the bone marrow. These processes must be quantified in order to

obtain an accurate estimate of the doses to the sensitive tissues in the skeleton.

5.1.2. The respiratory system

Radiation doses to the lungs and associated lymph nodes from inhaled plutonium compounds are based on the ICRP Task Group Lung Model using transfer fractions and rate constants given in ICRP Publication 19, 1972. There are no human data on the sensitivity of the lymph nodes to irradiation but animal data suggest they are not a primary site for the development of malignant change. The radiation dose to the lungs is at present calculated as the average dose to the pulmonary and tracheo-bronchial regions of the respiratory system plus the associated lymph nodes.

The TGLM is a generalisation which can be applied to a wide range of inhaled radionuclides. For its application to the dosimetry of inhaled plutonium there are a number of particular problems :

- a) Recent experimental data suggest that for Class Y compounds of plutonium the model overestimates the amount of plutonium translocated to lymph nodes and to the blood, this needs to be confirmed, particularly at low levels of exposure.
- b) The uncertainties in lung dosimetry would be substantially reduced if the sensitive cells could be identified, but these may vary from species to species.
- c) Large particles that are inhaled deposit predominantly in the nasopharyngeal region of the lung. There is no adequate information available from which to assess the local consequences of inhalation of large particles and the extent of absorption of radioactivity from the particles into the body.

5.1.3. The gastrointestinal tract

For alpha irradiation the radiation dose absorbed by the mucosal cell layer is assumed to be 1% of that at the surface of the gut contents. This is an arbitrary value and requires substantiating.

5.1.4. Quality factor

ICRP now use a quality factor (Q) of 20 to take account of the greater effect of alpha particles in causing damage to tissues than low LET radiation per unit of absorbed dose. There is only limited experimental justification for this value. More studies comparing the relative biological effectiveness of low LET radiation and alpha radiation, particularly for chronic exposures at low doses, would provide valuable data from which to determine the most appropriate Q for alpha irradiation of tissues.

5.1.5. Animal studies

Animal studies have demonstrated that the levels of deposition of actinides in tissues can influence clearance mechanisms. It is therefore important that to obtain results that can be extrapolated to man with confidence, levels of exposure of animals should be near to those equivalent to maximum permissible concentrations in man.

5.2. Toxicity

ALI's are based on dose limits for both stochastic and non-stochastic effects in tissues.

5.2.1. Stochastic effects

Animal studies are of value for identifying tissues and cell types at risk but because of species differences in sensitivity there are considerable uncertainties in extrapolating animal data to man. There are at present extensive toxicological studies underway in the United States in which the biological effects of actinides administered to dogs by intravenous injection or inhalation at varying dose levels are being studied. These studies are expensive and there is no justification for duplicating this effort in Europe. Studies on the toxic effects of actinides to be conducted in Europe should concentrate on studying mechanisms of carcinogenesis, identifying tissues at risk and investigating the merits of calculating average organ doses (the hot particle problem).

5.2.2. Non-stochastic effects

There is no information on non-stochastic effects in tissues induced by alpha irradiation at doses comparable to the non-stochastic dose limit (500 mSv (0.025 Gy) per year).

5.3. Operational problems

The adoption of ALI's for plutonium, shortly to be published by ICRP Committee II, will necessitate greater reliance on the estimation of intakes of plutonium by inhalation from measurements of air concentrations in the working environment. There are at present only limited data from which to extrapolate results obtained from high volume air samplers cascade impactors, personal air samplers, etc... to estimate actual amounts inhaled. Such data as are available need to be refined by further studies.

Systemic deposits of plutonium and other actinides are estimated from measurements of the rate of excretion in the urine. At present urinary excretion data for plutonium are based on data obtained by Langham from terminal patients given intravenous injections of plutonium citrate. There are difficulties in using these data to estimate systemic deposits. Thus at long times (5 years or more), the formulae developed from Langham's data appear to overestimate systemic deposits. Some chemical forms of plutonium, in particular small (\sim /nm) PuO_2 particles which enter the blood show an enhanced excretion. Animals experiments have also indicated that the urinary excretion of other actinides may be enhanced relative to plutonium. To improve the methods of interpretation of bioassay data further knowledge is therefore needed of the relationship between urinary excretion and systemic deposits. This can be obtained both from animal studies, from follow-up studies on occupationally exposed humans and by measurement of the levels of actinides in tissues taken at autopsy.

5.4. Plutonium in the environment

The values for the gastrointestinal absorption of plutonium that have been adopted by Committee II of ICRP are mainly based upon studies in which small animals have acutely ingested relatively large amounts of inorganic materials (PuO_2 , Pu nitrate, Pu citrate, etc.). There is only a limited amount of experimental data on uptake by large animals; on absorption following chronic ingestion of very low level or following the ingestion of actinides associated with plant and animal materials. It is possible that under these circumstances current estimates of absorption may underestimate the actual value. The presence of other valence forms of plutonium (e.g. Pu VI, Pu VII) may also significantly influence absorption. Few data are available on the higher actinides. Further studies are therefore required on the gastrointestinal absorption of actinides.

Other aspects of the behaviour of plutonium and other actinides in the environment that are little understood are :

- a) The mechanisms of binding of actinides to sediments in the fresh water or marine environment;
- b) The consequences of these sediments are subsequently suspended in the air and inhaled;
- c) The level of accumulation of actinides by food crops grown in ground contaminated by actinides.

There are very few data available from the countries of the EC on fallout levels of plutonium or other actinides either in drinking water, foodstuffs, or in members of the general public. These levels must be known if the consequences of exposures of the general public to actinides resulting from the nuclear power programme are to be adequately predicted.

5.5. Biological effects in man

A limited amount of information on the metabolism of plutonium and other actinides has been obtained from studies of plutonium workers. The data are difficult to interpret because many workers are also exposed to external radiation and possibly to other internally deposited radionuclides. From the small number of workers who have incorporated

plutonium or other actinides, there is no evidence of life shortening or malignant disease which can be attributed of these intakes. The total number of persons in the Nuclear Industry is increasing annually and long term follow-up studies of those exposed to plutonium and higher actinides could provide valuable information for improving the basis upon which standards of protection are determined. At present the collection of this data is very fragmented, member states should be encouraged to collect such data in a systematic way.

At present the methods available for removing accidental intakes of actinides from the body are only moderately successful. The development of methods for removing both soluble and insoluble forms from the body should be continued.

6. Radiotoxicity of Tritium

6.1. Introduction

Tritium is the radioactive isotope of hydrogen which is the most abundant element in the biosphere. In living organisms, tritium is partially exchangeable with hydrogen of macromolecules or may be incorporated at non-exchangeable hydrogen positions through specific metabolic pathways. Most of the tritium which is released to the environment of man is released in the form of THO to water and to air. From this part of the biosphere it may be incorporated directly or via the various aquatic and terrestrial food chains.

In the years to follow the already existing problems connected with the radiotoxicity of tritium will very probably become more important :

- The already existing public discussion on the tritium contamination of the local environment of nuclear fission power plants is likely to grow with the increasing number of these installations.
- The development of nuclear fusion as a new source of nuclear energy with a large inventory of tritium has reached a new stage with the positive decision on the Joint European Torus-programme.
- The public discussion of the risks of release of radioactivity from nuclear energy plants has already largely influenced the decisions on new nuclear energy installations and, with reference to tritium, might request detailed information long time before nuclear fusion is likely to become an economic energy source.
- The increasing production of tritium labelled organic compounds requires due attention as a source of radiation hazards in the local environment of industrial and research laboratories and hospitals.

The biological damage which may be produced by tritium depends on its relative abundance and its local distribution in the human body, its molecular localization, and its radiation quality. Both short term and long term radiation effects have to be considered. Their understanding requires insight into the different radiation mechanisms and attention should be focussed on areas of ecology, radiobiology, and dosimetry

which are particularly relevant to the protection of man and his environment against the radiation risk from tritium. It is obvious that chronic low level contamination hazards are of particular interest in view of the large populations that are possibly involved. However, also possible local accidental exposures require due attention because of the increasing sensitivity of the public for radiation hazards following reactor accidents.

6.2. Transport of tritium in different biological levels

The importance of this aspect of the total tritium risk depends on whether the exposure is chronic or acute.

For chronic exposure a situation of equilibrium is obtained in all inorganic and organic pools of the biosphere after several 100 days. In some terrestrial pools, such as the soil, this time may be considerably longer. In the case of equilibrium the turn over rates between the different pools are irrelevant for the evaluation of the radiation hazard. The relation of the amount of tritium in an organic pool to the amount of tritium in water, the so called isotopic factor, was found to be < 1 after THO exposure. However, for tritium offered through food chains from THO and from tritiated DNA-precursors, also isotopic factors above 1 were reported. Anyhow, most of the information available does not contradict the assumption that, under conditions of chronic exposure, an isotopic factor of 1 can be used for the estimate of radiation risk of tritium from THO for all organic pools. It must be stated, however, that only a few studies have been performed on the isotopic factor after chronic uptake of organically bound tritium, and the molecular formations of tritium were mostly unknown in these cases.

For acute exposure, e.g. due to a lithium fire accident in a fusion reactor, the input and output rates of tritium between the different inorganic and organic pools of the biosphere become very important. Most tritium is incorporated directly into the living tissues, in the form of tritiated water. The transfer of tritium from THO is largely by exchange with the labile hydrogen-atoms of organic fractions. Carbon bound hydrogens are

very stable and it requires enzymatic processes to produce a limited exchange between them and the hydrogen atoms of free body water. Consequently, after acute exposure of tritium in the form of THO, the transfer rate of tritium to organic molecules is high, however, only a very small part of tritium incorporated as THO or through the food chain may be bound to critical organic molecules like DNA. On the other hand, this small part is accompanied by fairly long half lives of several 100 days. Little is known about the half lives and the corresponding turn over rates within and between the ecosystem and different organic constituents in the human body. The situation is complicated further by the fact that the rate of incorporation from THO to organic tissue varies significantly with age and sex for mice. For strongly proliferating tissue, like the embryo, the incorporation rate is possibly at maximum. Therefore the question to the local radiation hazard of acute accidental exposures cannot be answered with the required certainty.

In addition, the public is much sensitized for the problems of possible reactor accidents followed by a release of radioactivity to the biosphere. Isotopic factors of 6 - 8 were found in the soil and of 3 - 4 in the vegetation. These results reflect the non equilibrium of the ecosystem after the stopping of atomic weapon tests in the atmosphere. But they are often incorrectly used as a proof for the enrichment of tritium in organic compounds and are certainly not suited for calming down the nervous reactions of the local citizens demonstration groups. On the other hand, the high isotopic factors in the soil, several years after the stopping of atomic tests in the atmosphere, show that the time constants describing the decrease of tritium in the different ecological pools have possibly been underestimated. Although it seems unlikely that the tritium dose commitment

after a fusion reactor accident will exceed the established critical levels it is evident that the connected ecological and radiobiological problems have to be investigated further. Such studies are also required in view of the increasing political difficulty for obtaining localization decisions and working permissions for new nuclear energy installations.

63. Tritium Localization and Biological Half Lives

The electrons emitted by disintegrating tritium atoms have a mean range of 1 μm and a maximum range of 6 μm . Therefore the amount of tritium present in the cell nuclei is the main source of radiation damage. Tritium in body fluids and in the cytoplasm does not contribute directly to the induction of damage. On the other hand, the entire nucleus lies within the maximum range of one tritium beta-particle from any part of a chromatide.

In the case of chronic tritium exposure the tritium distribution in the body can be regarded as fairly uniform as was discussed in the foregoing section. Special localization problems need not to be considered here.

For acute exposure of THO the input and output rates of tritium between the different inorganic and organic pools of the biosphere and the corresponding half lives are the essential parameters. Of special interest are those tritium atoms which are bound to C in DNA. However, also other long living pools of the biological tissue are possibly important. After acute THO exposure and for short term effects most of the radiation dose is due to tritium in the body water. Therefore special effects due to tritium in the DNA are in general dominated by the background radiation from THO. This is different, however, for long term effects. In this case, after acute exposure, the dose commitment of organically bound tritium may be much larger than that from THO.

Tritium labeled organic compounds, in particular labeled DNA precursors, may contribute directly to fixing tritium atoms in the genetic material. In general, about 10 % of

incorporated tritiated thymidine goes into the proliferating cell compartment and remains incorporated into the DNA of the cell or its descendants. For actively proliferating tissue, such as embryonic tissue, this percentage may rise up to 30 %. The remainder is catabolized to tritiated water and other non-volatile metabolites which may be re-utilized for the synthesis of DNA. Therefore this type of tritium source represents a special radiation risk in the local environment of producers and consumers, such as chemical industry, hospitals and research laboratories. For somatic radiation effects in vitro, after injection of tritiated thymidine corresponding to medium and high dose levels, the biological effectiveness was a factor of 3 - 4 greater than for acute exposure of THO. About the same factor was found for sensitive short term effects in vivo.

After experimental acute exposure with tritiated DNA-pre-cursors, genetic mutations have been shown to depend also on the particular tritium position in the DNA molecule. This must at least partly be due to additional non ionogenic effects, mainly the transmutation of ^3H to ^3He . There was no such position effect for somatic radiation damage in vitro.

6.4. Dosimetry and Radiation Quality

The beta-rays of tritium have a maximum energy of 18.5 keV and a mean energy of 5.7 keV. For a chronic exposure of THO and the corresponding homogeneous distribution within the body the annual dose is $1.1 \cdot 10^{-4}$ mrad per pCi/l. In case of a specific incorporation of this amount of tritium in only the cell nuclei of the human body, and for low doses, this value has to be multiplied by more than 3. If the tritium is only distributed within the body water, such as e.g. in case of short term acute exposure of THO, the above figure has to be multiplied by 0.7. The mean dose due to a single disintegration of tritium in the nucleus of an average human cell of 8 μm diameter is 0.3 rad. Low dose means

that on the average there is less than one disintegration per cell nucleus, hence that the absorbed dose is smaller than 0.3 rad.

The radiation quality of tritium beta-rays, as measured by the microdosimetric parameters \overline{y}_D and \overline{y}_F , is about equal to the radiation quality of 65 kV X-rays for sensitive volumes of 0.5 - 3 μm . There is reason to assume that this radiation quality of tritium is in agreement with experimental RBE-values in vitro of 1 - 2 relative to 200 kV X-rays and of 2 - 4 relative to ^{60}Co -gamma rays. Also the observed dose dependence of RBE of in vitro experiments agrees with microdosimetric theoretical calculations.

There is no experimental evidence that the radiation quality of tritium may be different from that of 65 kV X-rays as far as short term effects in vivo are concerned. Also in comparison with other X- and gamma-rays short term effects in vivo are likely to be qualitatively equal, however, their time dependence might be different for different low LET-radiations.

Also for long term effects no definite answer to the radiation quality problem of tritium is possible at the moment. The experimental data of tumor induction in mice are at variance and seem to reflect different sensitivities of the mouse strains investigated. However, it is not impossible that the spectrum of the induced tumors depends on the chemical compound in which tritium is administered. If so, such carcinogenic action of tritium might conceivably be related to its particular site of intracellular incorporation rather than to radiation quality.

For genetic effects the particular location of tritium in DNA does play a significant role.

Thus it appears that the geometrical position of the tritium atom in the DNA, and the ways of energy transfer to the neighbouring sensitive structures need to be considered. This requires further investigations of transmutation effects, but also microdosimetric studies on the geometric

and statistical overlapping of the pattern of radiation structure and of the radiation sensitive biological structures at molecular levels. The most important electrons for the local energy deposition, say within 10 nm, are the electrons of about 1 keV. In this low energy range the beta-ray spectrum of tritium is very uncertain.

6.5. Radiation and Repair Mechanisms

Investigations on radiation effects in DNA and on the mechanisms that are involved in the repair of radiation damage of DNA are usually not of immediate practical concern for radiation protection. However, they are fundamental prerequisites for the interpretation of radiobiological experiments in general and for our understanding of the primary mechanisms leading to the observed radiation effects, in particular long term effects. Therefore studies on the molecular anatomy of DNA-damage by tritium and on the modalities of its repair are a necessary complementation of any larger programme on the radiation toxicity of tritium. Our current understanding indicates that

- repair of radiation damage of DNA may be influenced by radiation dose and may depend on radiation quality,
- premutational lesions may be fixed in the genetic material through unscheduled and non-functional rejoining events,
- point mutations are also introduced by errors in the rapid reactions,
- induction of repair mechanisms by radiation at medium dose levels may facilitate viral transformation of cells.

6.6. Short-Term Effects in Vivo

The survival probability of oocytes in the ovaries of mice is considerably reduced after acute and protracted exposure to THO and tritiated thymidine, corresponding to total absorbed doses of several rad. The DNA-bound tritium is about 4 times more effective than the THO which is homogeneously distributed. No information is available so far on the ef-

fectiveness of low doses of tritium and on the RBE of tritium in relation to external X- or gamma-rays.

The reduction in hematopoietic stem cells with the maintenance of normal cellularity is similar to that seen for partial body and whole body single X-ray exposure. Further investigations on the disfunctioning of bone marrow stem cells are necessary, in particular for chronic tritiated water ingestion.

.7. Long-Term Effects

The long-term toxicity of tritium in living tissues, and particularly in mammals, is largely unknown. A few experimental observations exist on the carcinogenesis and life shortening of mice following acute and chronic exposure with THO and tritiated thymidine in the range of 0.3 - 5 $\mu\text{Ci/g}$ body weight. For new born mice the increase in the overall tumor incidence was highest and there was a definite modulation in the tumor spectrum. Data on adult animals were ambiguous.

Very little is known about the relative contribution of the time sequence of dose during the usually long latency period after acute exposure. In mice that exhibited an increased tumor incidence following administration of tritiated thymidine at birth, an average residual activity of about 3 % per animal was found during the last third of the life span. Whether the carcinogenic action was triggered by this final dose level, which contributed to most of the commitment dose and was much higher than for THO, or by the initial exposure, which was much larger in dose rate, remains unsolved.

As far as the comparison with other radiations is concerned it was already explained in section 4 that the data are ambiguous and no conclusion with regard to the radiation quality of tritium for long term effects is possible.

Thus much more experimental data is needed on the comparative carcinogenic yield of THO, tritium labeled precursors, and external radiations, both for chronic and acute exposures.

6. 8. Detection of Tritium

The low energy of the electrons emitted by tritium has required the developement of many detection devices with individual specifications for each particular monitoring requirement. The developement resulted in successful readout monitors and collection systems, the possible improvement of which is, and has to be, continously investigated.

In contrast to the physical detection of tritium the biological detection is still in its infancy. In case of an accidental incorporation of tritium of unknown chemical formation both the dose commitment and the type of tritium source has to be analyzed and estimated in a sufficiently small time. The knowledge of the original chemical formation is necessary because it influences the dose commitment and possibly the RBE. With the techniques now available the evaluation of the chemical compound of the incorporated tritium is not yet possible, and also the dose commitment can not be calculated with the required certainty. First investigations looking pragmatically for the possible thumb-prints of DNA-and RNA-precursors in urine have hardly been successful. However, in view of the importance of this problem for practical radiation protection, these investigations have to be continued looking not only to excretion but also to promising tritium pools of the body, such as blood.

6.9 RECOMMENDATIONS

After having considered the status of existing knowledge and of current research on the radiotoxicity of tritium, as well as foreseeable trends and demands of protection against chronic and acute tritium exposure, it is recommended to execute an appropriate research programme in the following areas of tritium

ecology, radiobiology, dosimetry and detection:

- Transfer of Tritium between Different Biological Levels

Current information on the isotopic effect of tritium offered through food chains from THO are contradictory. Therefore such studies have to be continued. In particular, the isotopic factor for tritium in organic pools following the incorporation of tritium through the food chains or via labeled biomolecules must be investigated.

The half lives and intake rates of tritium in the different pools, particularly in the organic pools of the body, have to be investigated further. Such data are fundamental prerequisites for the assessment of radiation hazards from accidental tritium exposure.

- Effects of Special Molecular Localizations of Tritium

The short- and long-term effects of labeled organic molecules which result in the fixation of tritium at certain positions in the DNA must be investigated further. The corresponding risk factors, in particular after acute exposure, have to be evaluated.

- Modalities of DNA-Repair after Tritium Damage

Investigations on the molecular anatomy of DNA-damage and on the modalities of its repair are a necessary complementation of the studies on special molecular localization effects. These investigations will help to elucidate the primary mechanisms leading to genetic and cellular transformations and to tumor induction.

- Short-Term Effects in Vivo

Radiation damage to oocytes, after acute and protracted exposure to THO and tritium labeled biomolecules, has to be investigated further, in comparison with external X- or gamma-rays. It is desirable to extend these studies to lower doses.

Further investigations of the disfunctioning of bone marrow stem cells are necessary, particularly for chronic tritiated water ingestion.

- Long-Term Effects

Information on long-term effects after chronic exposure to tritium is scarce and contradictory. Further studies on the different carcinogenic action of THO and of tritium labeled biomolecules are required, looking to the increase in the overall tumor incidence and to changes in the tumor spectrum.

Investigations of the tumor induction after acute exposure to THO and to tritiated biomolecules have to be continued regarding in particular the possible correlations between the tumor incidence on the one hand and dose commitment or initial dose rate on the other.

For both, chronic and acute exposures, much more experimental data is needed on the comparative carcinogenic yield of tritium and external radiations. In these investigations it should be tried to extend the results to as small doses as possible.

- Microdosimetry

The local distribution of energy deposition around a single disintegrating tritium atom and the probabilities of damaging the surrounding relevant molecular bonds have to be investigated. These studies are related to the different effects after specific incorporation of tritium at certain positions in the DNA and to the possible contributions of ionogenic and non-ionogenic effects.

The calculation of microdosimetric spectra and parameters of tritium has to be extended to smaller dimensions, and the knowledge of the beta-ray spectrum of tritium has to be improved at the low energy side.

- Detection of Tritium

Biochemical methods have to be developed which are needed for the identification of the chemical compound of the incorporated tritium after accidental exposure.

Also the methods delivering the data for the evaluation of the dose commitment of tritium have to be improved.

GENETIC EFFECTS OF IONIZING RADIATION

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GENETIC EFFECTS OF IONIZING RADIATION

1. Introduction

The importance and significance of the study of radiation effects on genetic material stem from the fact that radiations may increase the incidence of chromosomal syndromes and of hereditary diseases and that only detailed analyses of the complex pathways through which the irradiated cell deals with pre-mutagenic and pre-carcinogenic lesions will provide the necessary data-base that can be used in radiation protection and hazard evaluation. Thus, the general objectives in this sector are to provide the information needed for:

- assessing in humans, and when necessary, in experimental species, the role of factors which govern, modify or prevent the establishment of damage. The research carried out in the past now renders possible the genetical and biochemical characterization of some of the processes of DNA repair in human cells. A stimulation of the research on the elucidation of mechanisms may not only allow a continuation of this work but, ultimately, it could provide new means for predicting interactions between damages and effects, for establishing relationships between mutagenesis and carcinogenesis and for preventing or protecting against radiation damage. It should also accelerate the development of methods for the detection of sensitive individuals and, among these, of individuals who are heterozygous for genetic diseases involving a repair deficiency and who may have an increased sensitivity to mutagens and carcinogens.
- evaluating, through the use of the methods currently available (direct and doubling dose methods), the genetic damage induced by radiation in man. The information required for this purpose includes estimates on the birth frequencies of genetic diseases, the magnitude of doubling dose(s) and the induction rates of genetic defects per rad.

The documentation and evaluation of problems presented below are intended to provide the background necessary for an assessment of the present state of knowledge and of approaches which could be used for reaching the objectives of the Commission programme 1980-1984. The reviews prepared for each of the three sub-sectors (biochemistry and genetics of sensitivity and repair; assessment and analysis of genetic damages in

eukaryotes; dose-effect relationships) constituting the sector on genetic effects are of different lengths because a substantial portion of the relevant scientific documentation for certain sub-sectors is being published or edited elsewhere as special reports from the Commission.

2. Sub-sector on the biochemistry and genetics of radio-sensitivity and repair

The genetic information which enables a cell to function is encoded in the nucleotide sequence of DNA. Not all primary changes induced in DNA by hazardous chemicals and radiations come to expression as mutations; the primary damage must pass through several cellular steps or sieves that exist in biological systems and which act to reverse or nullify the deleterious actions of these agents and only a small fraction of the initial changes survive to reach the stage of giving a mutant clone.

The evolution of such cellular processes in biological systems is not surprising in view of the variety of physical and chemical agents that have always been in the environment and of which some adversely affect DNA. Neither is it surprising that repair mechanisms are not always perfect but have allowed some mutagenic events to be realized thus enabling organisms to evolve. It is also to be expected that the repair systems themselves have been subject to evolutionary pressure.

The presentation, below, of the various processes and mechanisms which lead to the induction of damage and of its repair, and particularly those described in microorganisms, are extremely complex and may appear, at first sight, to bear only little relevance to a programme devoted to the radioprotection of man. In reality, however, it is obvious that the modern approach to the protection of man will be based upon our knowledge of his molecular biology (for specific examples see, below, at the end of this chapter and see also J.L. MARX, Restriction enzymes: prenatal diagnosis of genetic diseases, Science 202 : 1068-1069, 1978; C. de DUVE, Cellular and molecular biology of the pathological state, Report of study contract C.E.C., 1978). It is equally obvious (for instance, see table 1) that our capacity to understand the molecular biology of man has depended in the past and will depend in the future upon the analyses and exploratory studies which are first carried out on appropriate experimental species, and particularly microorganisms, where the initial clues can be found, the necessary methods established and the potent tool of genetic analyses used.

DATES OF DISCOVERY

	BACTERIA	HUMAN CELLS
Excision repair		
- Dimer excision	1964	1966
- Unscheduled DNA synthesis	1964	1968
- Deficient mutants	1958	1970
- Host Cell Reactivation	1958	1970
Enzymes		
- Endonuclease	1964	
- Exonuclease	1970	1976
- Ligase	1968	1970
Photoreactivation	1947	1974
Base-excision	1972	1974
Recombination repair (mutants)	1966	X-P variants ?
Error prone repair	1953	1978
Inducible repair	1970	1978
Mismatch repair	1972	1977/78

Table 1. Examples of the importance of research with microorganisms (in the present illustration, bacteria) for the elucidation of repair mechanisms in man. Basic discoveries in man have always been preceded by the identification of similar processes (and the elaboration of specific techniques) in microorganisms.

In the section which follows on the present state of knowledge, repair and sensitivity are discussed under three major headings reflecting the contributions obtained from work with (1) Prokaryotes (particularly Escherichia coli), (2) Lower Eukaryotes (particularly yeast) and (3) Higher Eukaryotes (particularly human cells).

2.1. Present state of knowledge

2.1.1. Contribution from work with prokaryotes

The data obtained from studies on the UV-induced dimers in the DNA of E. coli indicate three main mechanisms for efficient repair: photoreactivation, excision repair and postreplicative repair.

2.1.1.1. Photoreactivation

Photoreactivation is a specific repair process carried out by a single enzyme (EC 4.1.99.3, photolyase or photoreactivating enzyme) which binds to pyrimidine dimers, and in the presence of visible light (300-600 nm), splits the cyclobutane ring in situ. This monomerization process thereby restores the two pyrimidines to their original configuration. In E. coli a mutation (phr) in the gene coding for this enzyme produces a mutant phenotype lacking the ability to photoreactivate its own or phage DNA.

2.1.1.2. Excision repair

Unlike dimer-specific photoenzymatic repair, the excision repair process can act upon a large spectrum of chemically distinct lesions induced by both physical and chemical agents. Excision repair defines a set of pathways in which damaged bases are removed either as free purines and pyrimidines or as nucleotides.

The isolation of a bacterial mutant deficient in repair occurred as early as 1958 when Hill isolated a radiation sensitive mutant (B_{s-1}) from E. coli B. The loci uvrA, uvrB (B_{s-1} is mutated at this locus) and uvrC were the first of a large number of genetic loci which, subsequently, were shown to affect the sensitivity of E. coli to radiation.

Comparative studies of strains bearing these mutations, with wild-type strains, designed to elucidate the basis of wild-type resistance, led to the discovery in 1964 of DNA excision repair. The most widely accepted model for this multienzymatic process consists of four coordinated steps which are described in details in the document prepared for discussion at the meeting of C.E.C. contractors at Gif-sur-Yvette (January 24-25, 1979). These four steps involve action by :

- a highly specific endonuclease which detects a lesion-containing site and incises the damaged strand in the vicinity of the defect;
- an exonuclease which introduces a second scission and releases the lesion;
- a normal DNA polymerase which inserts into the gap normal nucleotides complementary to those on the opposite undamaged strand (repair DNA synthesis);
- last, a DNA ligase which binds the host inserted nucleotide and the pre-existing one in juxtaposition.

An alternative mode of excision-repair, termed "base excision repair" in contrast to the classical "nucleotide excision repair", has recently been discovered. The damaged base is released by a glycosylase and the resulting site of base loss is subject to attack by an endonuclease.

2.1.1.3. Postreplication repair

The mechanisms above are concerned with removing damage from DNA before replication. However, in many cases, lesions are not all removed from DNA and the way in which cells survive lesions remaining in their DNA during replication is termed postreplication repair. If pyrimidine dimers are present in the template strand during DNA replication, the extension of the growing chain by DNA polymerase III is halted. Then, bypass mechanisms become operative and synthesis recommences at the next RNA primer site. As a result, newly-synthesized DNA contains gaps at about the frequency of the spacing between dimers in DNA. One mode of bypass which is consistent with current data, implicates the transfer of genetic material from parental to daughter strands of the DNA (recombination repair with the opposite daughter duplex) with some remodelling-polymerization

at the ends of the exchanged segments. The resulting gap of the parental strand may then be filled in by repair DNA synthesis. The genetic material can thus be replicated while containing a damaged site. Subsequently, the dimers may be excised and the gap repaired.

Postreplication repair does not occur in recA strains of E. coli, which are deficient in recombination. The exact details of this type of repair are not known but the active roles of the recB⁺/recC⁺ genes, ATP-dependent DNAase and of polC (DNA polymerase III) are generally recognized. Finally, in E. coli evidence has been presented recently to suggest the existence of a new error-free excision-dependent post-replication repair of potentially mutagenic overlapping daughter strand gaps (ODSGs). Strains bearing the mutations mfd or dnaB have some properties consistent with a deficiency in such a pathway. For example, the phenotypes of both show elevated mutation but little increase in radiation sensitivity and these properties are not expressed in a uvr background.

2.1.1.4. Repair of DNA damage specifically produced by ionizing radiation

The above biochemical systems are also implicated in the repair of DNA lesions of X- and γ -irradiated cells. Specific modifications of the outlined pathways occur for different molecular and conformational changes. Evidence for repair of γ -induced base defects in E. coli has been indirectly obtained with the aid of enzymatic assays, utilizing crude extracts from Micrococcus luteus as the source of ϵ -endonuclease activity required for detection. Gamma-endonuclease sensitive sites have been found to disappear from plasmid DNA in E. coli much more rapidly than do UV-endonuclease sensitive sites, suggesting that the γ -radioproducts are acted upon by a repair mechanism differing in at least one step from the one operating on pyrimidine dimers. The demonstration that a uvrA strain of E. coli, defective in dimer excision, eliminates ϵ -endonuclease-sensitive sites with normal kinetics supported the existence of a second endonuclease.

In E. coli, studies with radiation sensitive mutants have revealed at least two repair processes presumably acting on different types of breaks. A fast repair process rejoins the majority of breaks

within a few minutes of irradiation. DNA polymerase I and DNA ligase are probably the only enzymes involved and rejoining can take place in buffer at room temperature.

Radiation nicks in DNA chains do not always carry the biochemical termini (3'-OH/5'-P₀) which are required for closure by DNA ligase. With other termini a trimming and cleaning operation has to be carried out by competent enzymes to transform the nicks either into functional 3'-OH/5'-P₀ internucleotide scissions or into gaps repairable by the combined action of DNA polymerase and ligase. The biochemical findings suggest that the misrepair of radiation nicks in DNA by ligase may contribute significantly to the inactivation and death of cells exposed to ionizing rays.

A small minority of the breaks, however, can only be sealed by a slow much more complex process requiring full growth conditions, proteins synthesis and the intact products of several genes. These genes include polC⁺ (DNA polymerase III), lexA⁺, recB⁺/recC⁺ (exonuclease V) and recA⁺.

2.1.1.5. Error-prone repair

On the whole the three processes defined above appear to be accurate and all detectable mutations induced by agents such as UV probably arise through the operation of another non-recombinational error-prone repair pathway. It would seem that only certain types of DNA damage are substrate for error-prone repair and in E. coli this process is strictly dependent upon the lexA⁺ and recA⁺ genes. The involvement of the recA⁺ gene seems to be due to a requirement for its product for any type of process that involves a sizeable single-strand DNA gap although recA⁺ lexA⁺ error-prone repair can act at sites other than daughter strand gaps such as in excision repair.

It is interesting to note that DNA polymerase III (coded by polC⁺) is needed for this process whilst in all other types of repair requiring polymerase action, polymerase I and/or II can substitute for polymerase III. It is generally believed that error-prone repair is not constitutive but that damage to DNA or interruption of its replication (polymerase idling) induces

among other functions an error-prone DNA polymerase activity (SOS repair) which is responsible for UV mutagenesis in E. coli. An alternative hypothesis has been suggested, based on the assumption that newly-synthesized DNA is 'immune' to error-prone repair for a certain period of time after which those gaps not susceptible to error-free processes are still available and can act as a substrate for error-prone repair.

A number of other phenomena associated with DNA damage are also recA⁺ and LexA⁺ dependent ('inducible' rec-Lex functions). These include (i) filamentation resulting from inhibition of cell division in lon strains of E. coli, (ii) induction by DNA damage of vegetative growth of a lysogenic prophage such as λ , (iii) induced reactivation (Weigle reactivation or UVR) - increased repair and mutagenesis of extracellularly-irradiated phage λ following mild irradiation of the host cell, (iv) protein X formation - a protein of molecular weight 40,000 daltons (which is now recognized as the product of the recA⁺ gene) synthesized in large amounts following irradiation, (v) exonuclease V inhibition - the formation of an inhibitor of DNA breakdown following ionizing radiation can be deduced from split dose experiments, (vi) respiration failure - following irradiation an apparently lethal inhibition of respiration, associated with NAD depletion, can be demonstrated under certain growth conditions. A number of other genes or alleles affect expression of rec-Lex functions. In tif mutants (tif is a probable allele of recA) SOS functions (including SOS repair activity) are thermally inducible, although DNA structure and replication are apparently normal at elevated temperatures. When grown continuously at 42°, tif strains exhibit a striking mutator effect indicating that the derepressed SOS repair increases the error-proneness of normal DNA replication. Also, thermal treatment of tif populations, even in unirradiated cells but even more so after mild irradiation, enhances mutagenesis far above the background level. The likely interpretation of this is that an error-prone DNA polymerase activity is induced which increases the frequency of spontaneous mutations by making normal DNA replication more error-prone but that the same activity acts with a much higher probability of error at specific target sites resulting from radiation damage which are not subject to repair by constitutive error-proof mechanisms. Other genes affecting SOS

functions include lexB and zab (probably alleles of recA resembling lexA in phenotype i.e., blocks radiation mutagenesis and some gap-filling processes); sfi (suppressor of filamentation) which partially reverses the tif phenotype and different sfi mutations have differential effects on rec-lex functions; tsl (temperature sensitive suppressor of lex) and rnm (resistant non-mutable) which partially, and in different ways, reverse the lexA phenotype; polA polymerase I), dnaB (conferring temperature sensitivity to DNA synthesis) and dam (deficient in general methylation of adenine in DNA but not in methylation required for modification of DNA).

A specific protease has been shown to be involved in λ phage induction and the lon⁺ gene may code for another such protease. The suggestion has, therefore, been made that the SOS 'system' involves the co-ordinate de-repression of a number of unlinked genes by a common induction signal. It also seems likely that proteolytic cleavage is a necessary step in this de-repression since the specific protease inhibitors antipain [(1-carboxy-2-phenylethyl) carbamoyl-L-arginyl-L-valylargininal], and TLCK (tosyl-lysine chloromethyl ketone) as well as purified λ repressor protein inhibit λ prophage induction and drastically decrease mutagenesis. At least one form of protein X (the recA⁺ gene products) shows protease (endopeptidase) activity and this could account for the occurrence of lysogenic induction. Although the exact role of recA⁺ in repair and recombination remains unresolved a clue has been provided by the demonstration of the binding of the recA⁺ product to single stranded DNA. It has recently been suggested that protein X is a DNA dependent ATP which stimulates the reassociation of DNA.

In addition to radiation and chemical mutagens (e.g. mitomycin C) a number of other agents including the potent carcinogen aflatoxin B and the antitumour drug PDD (cis-platinum(II) diaminodichloride) have been shown to induce lesions in DNA and to act as inducers of SOS functions in E. coli. Moreover, the plasmid pKM101 is known to enhance the SOS system and to cause an increased mutation frequency.

It is thus clear that in E. coli there are two major pathways responsible for mutagenesis : i) the 'indirect' pathway via the

recA dependent SOS repair system discussed in 2.1.1.4. above and ii) the 'direct' pathway encompassing both spontaneous and recA independent mutagenesis resulting from direct modification of the DNA template itself. The latter pathway has been investigated after treatment of cells with a wide variety of mutagens but especially base analogues (e.g. 2-aminopurine and 5-bromouracil) and deaminating agents (e.g. hydroxylamine and nitrous acid). The correction of mispairing lesions produced by these chemicals seems to occur at two levels; one directly following precursor incorporation in a 3'-5' exonucleolytic proofreading reaction by DNA polymerase itself (see section 2.1.1.2. above) and the other which depends on mismatch repair analogous to gene conversion. Interestingly, recent data are consistent with the hypothesis that 6-methyladenine residues in E. coli DNA are involved in strand discrimination during this mismatch correction.

Another important finding from the work with chemicals, particularly if it proves to be more general, is that of 'adaptation' to alkylating agents where the growth of E. coli in the presence of low concentrations of these chemicals can cause resistance to the lethal and mutagenic effects of high concentrations. This observation suggests that inducible error-free as well as inducible error-prone repair systems exist in E. coli.

Investigations of radio-sensitive mutants and DNA repair process in other prokaryotes (Mycoplasma, Micrococcus, Gloeocapsa, Bacillus, Salmonella) support the results obtained from E. coli. Minor differences are outlined in the discussion document for the C.E.C. meeting at Gif.

2.1.2. Contributions from work with lower eukaryotes

The yeast Saccharomyces cerevisiae and Schizosaccharomyces pombe are among the simplest eukaryotic organisms and much is known of their life cycle and genetics both at the nuclear and mitochondrial levels. These unicellular organisms have a sexual cycle and haploid and diploid mitotic phases; moreover polyploid isogenic strains are available. Under proper conditions meiosis is triggered and

the four products of meiosis can be recovered for analysis. These features make it possible to carry out extensive genetic analysis and to construct nuclear and mitochondrial genotypes for experimental purposes.

This genetic versatility of yeast with fast breeding cycles involving synchronizable mitosis or meiosis and their well established systems of nuclear and mitochondrial inheritance make this organism especially advantageous for inquiry into the significance of DNA protection and repair. It has been used for more than two decades in classical radiobiology as a model eukaryotic system and more recently as one of the powerful screening systems in environmental mutagenesis. The very recent and fast developments in the cloning of the yeast genome via bacterial plasmids or phages and the success obtained in yeast transformation with such vectors have opened an entirely new field of investigation.

In the last ten years about 55 independent loci capable of affecting yeast sensitivity to radiations and/or chemical mutagens have been identified. Most of the work done with sensitive mutants concerned radiation and chemical induced lethality, mutagenesis, intra and intergenic recombination and, more recently, chromosomal loss or non-disjunction in comparison with responses of original wild types.

Studies with multiple mutants have revealed the existence of four epistatic groups of genes associated with four categories of repair pathways which may overlap in certain steps. One group contains at least 9 genes which govern excision of ultraviolet-induced pyrimidine dimers. The second group controls an error-prone repair pathway and some of the loci in this group not only affect mutagenesis but are also required for the successful completion of meiosis. The third group of genes govern the repair of X-ray-induced double-strand breaks. In this group, pleiotropic effects such as alterations in spontaneous mutation rates, induced recombination, meiosis and spore-viability have also been described. Finally, from indirect genetic evidence the fourth group of genes appears to be required for post-replication repair.

Some of the significant concepts/ideas that have emerged from these studies are the following :

- a) The number of distinct genetic loci which affect sensitivity to UV and X-rays and also to alkylating agents such as methylmethane sulphonate is strikingly large in such a relatively simple eukaryote. It has been shown that inhibition of DNA repair is certainly involved for a number of the sensitive mutants in yeast but it is also likely that some of these gene products affect the response to radiations through regulatory processes.
- b) Some of the loci involved in the control of repair are extremely pleiotropic. They may simultaneously affect several diverse functions such as spontaneous and induced mutagenesis, recombination, meiosis and spore viability, some of the mitotic cell cycle parameters and cross-sensitivity to a variety of chemical agents. This leads to the notion that apart from their role in repair of radiation induced damage, some of the repair enzymes play a key role in other vital functions.
- c) At present, yeast cells are the only eukaryotes in which double-strand breaks (DSB) and their repair can be studied at the radiation doses which are used for survival studies. They are thus ideally suited for the analysis of relationships between DSB and lethality.
- d) Recent evidence suggests that some UV sensitive mutants may belong to more than one repair pathway. In view of this apparent relationship between repair pathways, the conceptually rigid distinction between the repair modes should be revised in terms of timing & coordination of enzymatic complexes and of spatio-temporal interactions between the substrate (DNA containing lesions) and such complexes.
- e) The analysis of the evolution of radiosensitivity in a synchronized cell-cycle indicates that the chromosomal configuration (end of S phase and G_2 radioresistance) as well as the integrity of specific repair pathways are both involved in the cyclic fluctuations.
- f) The mitochondrial genome of yeast provides an additional system of evolutionary and metabolic significance for the study of repair and recombination as well as for the nucleo-cytoplasmic relations to repair functions. A controlled excision of pyrimidine

dimers from mitochondrial DNA does not occur in yeast (the same is true for mammalian cells). The efficient recombination which is taking place in normal replication of yeast mitochondrial DNA appears to be the major replicative bypass process for UV-induced lesions.

- g) Finally, recent work has indicated that inducible repair function(s) involved in both mutation and recombination do exist in yeast. In addition to yeast, several other lower eukaryotes, and particularly Aspergillus, Ustilago, Neurospora and Chlamydomonas, have greatly contributed to our knowledge of repair processes. The major findings made on these organisms are outlined in the discussion paper studied at Gif-sur-Yvette during the meeting of C.E.C. contractants.

2.1.3. Contributions from work with higher eukaryotes (and particularly human cells)

2.1.3.1. Human cells

The importance of DNA repair in man is illustrated dramatically by a number of hereditary diseases that are accompanied by an increased sensitivity to radiation and incidence of cancer in the patients. With regard to human skin, epidemiological work now suggests that the incidence of at least squamous and basal cell carcinoma is largely dependent on geographical, climatic and anatomical factors which determine the amount of light penetrating the skin. Experimental work has shown that in the absence of sensitizing substances, light of wavelength greater than 320 nm is essentially non-carcinogenic. Since sunlight of wavelengths shorter than 290 nm is filtered out by the outer layers of the atmosphere, it seems reasonable to consider wavelengths of 290-320 nm as the most likely cause of actinic cancer in man. Patients with the recessive autosomal condition, Xeroderma pigmentosum (XP) are specifically sensitive to these short wavelengths. The exposed skin of these individuals, in the first few years of life, undergoes the changes (except elastosis) which are characteristic of solar induced degeneration. These are normally observed only in old people who have received very high cumulative doses of sunlight.

After a brief phase, marked only by acute sunburn episodes and by photophobia, XP patients begin to show permanent skin abnormalities such as dyschromia, atrophy and telangiectasias on the exposed part of the body. These are followed by neoplastic growths which start from multiple foci and continue to occur, often causing the patient's death in the second or third decade of life. Clinically, XP is an heterogeneous syndrome in which, beside the skin symptoms, neurological disorders are also involved in many cases. There can be a wide range of neurological abnormalities, the extreme of which is the de Sanctis Cacchione syndrome showing choreoathetosis, senso-neural deafness, sexual disfunction and mental retardation.

XP was the first radiation-sensitive human syndrome to be studied at the cellular level. From the work with bacteria it was suspected that deficiency in any of the repair mechanisms required for removal of UV-induced pyrimidine dimers might be involved. Although photoreactivation can be demonstrated to a limited extent under one restricted experimental condition in human cells in culture, it appears that it represents a vestigial function and is not likely to be of general importance. Approximately 80-90 % of all XP patients are defective in excision repair and most probably in its first step - the recognition of lesions and incision of DNA by endonuclease nicks. For example, it has been shown that the treatment of XP cells to render them permeable to an UV-specific endonuclease of viral (T4) origin resulted in uptake of the enzyme and a regaining of the capacity to perform excision repair. Thus it appears that once the block to the first step of excision repair is circumvented the remaining steps can proceed. XP cells are also more sensitive than cells from normal individuals to the lethal effect of UV and some chemical mutagens although they have normal sensitivity to ionizing radiation and can seal radiation-induced DNA strand breaks at normal rates. Most XP cells are more sensitive than normal cells to chromosome aberration production. The frequencies of sister chromatid exchanges (SCEs) in undamaged XP cells is the same as in normal cells but is higher than in normal cells following exposure to UV light, alkylating agents and other chemical mutagens. The ease with which defective excision repair can be tested has allowed the successful prenatal diagnosis of XP in amniotic cell cultures of fetuses at risk.

As more fibroblast cultures from XP patients were investigated what appeared to be a biochemically homogeneous disease was shown to be far more complex. Classifications made on the basis of clinical symptoms have been further sub-divided on the basis of biochemical observations. Although among common XP patients the majority show defects (with a range from 2-50 % of normal values) in excision repair of UV damage, a small group can be distinguished, (known as XP variants) which have normal excision repair of UV damage but an abnormally slow postreplication repair system. Most XP variant cells have normal UV sensitivity while a few show enhanced sensitivity but killing in all cells is enhanced greatly by incubation in caffeine after irradiation. There is good evidence that XP and XP variant cells are very sensitive to the mutagenic effect of UV light, thus providing support for the mutation theory of cancer.

The XP cells from different complementation groups, as well as from the variant, have been assayed for the presence of different enzymes of DNA metabolism, particularly the DNA polymerases α , β , γ and DNA ligase. These enzymes have been found present at levels within the variability of normal population.

It had been found that when fibroblasts of certain pairs of XP cells were fused to give heterokaryons, these acquired the ability to perform normal levels of unscheduled DNA synthesis (UDS indicates repair replication) and thus a deficiency in excision repair in one XP nucleus had been complemented by products of the other XP nucleus. This approach was utilized to examine the genetic heterogeneity of XP and the results demonstrated that at least seven genetically different forms for XP exist. In the former case at least five complementation groups are concerned with the UV-endonuclease step but the interpretation of the roles each play remains speculative. Suggestions arising from these results include a) that there is a complex system of genetic control of repair, b) that there are multiple subunits for the human UV endonuclease, c) that a number of cofactors are required for repairing damage in chromatin.

A second well defined human syndrome that seems attributable to DNA repair deficiencies is the autosomal recessive disease ataxia telangiectasia (AT). Ataxia telangiectasia is characterized

by cerebellar ataxia, telangiectasia, IgA deficiency in many cases, an increased frequency of malignancy and an enhanced level of spontaneous chromosome instability in lymphocytes and fibroblasts. Following initial reports of mortality ensuing in AT patients very shortly after treatment with conventional radio-therapy, it was demonstrated that fibroblasts from AT patients were highly sensitive to the lethal effect of ionizing radiation. These fibroblasts can also mend UV damage normally and rejoin single- and double-strand breaks. SCE frequencies are induced to the same extent as in normal cells by a variety of chemical mutagens. Excision of some unknown X-ray induced lesions (those showing an OER of 1.0) is slower than normal in some AT cell lines but both normal and AT cells are more sensitive to irradiation in oxygen than in nitrogen (OER about 2-3). Defects in the repair of γ -ray induced base damage have been reported for some but not all AT strains. Mutation induced by ionizing radiation has not been detected in AT cells, although they are mutable by UV.

Cell fusion studies have demonstrated that at least two complementation groups exist for AT indicating genetic heterogeneity in the disease. In view of the coincidence in AT of abnormal DNA repair and immunodeficiency, a test of whether or not the repair defect is functionally significant in lymphocytes as well as fibroblasts has been made. DNA repair capacity as measured in phytohaemagglutinin-stimulated lymphocytes from AT homozygotes after exposure to ionizing radiation was considerably reduced in comparison with normals.

Heterozygotes for AT, although lacking in the main clinical features of the syndrome do share a high predisposition to cancer. On the basis of an incidence of 1/40,000 for AT homozygotes, the heterozygotes would represent 1 % of the population and these cannot be diagnosed clinically. However, one study has demonstrated the laboratory identification of heterozygotes for AT based on the sensitivity of lymphoblastoid cell lines to ionizing radiation.

Apart from XP and AT a number of other congenital diseases have been proposed as subjects for studying deficiencies in DNA repair. These include basal cell naevus, Bloom's syndrome,

Cockayne's syndrome, dyskeratosis congenita, some forms of diabetes, Fanconi's pancytopenia (Anaemia), Hutchinson-Gilford's syndrome (Progeria), Rothmund's syndrome, Thomson's syndrome, Werner's syndrome, Wiskott-Aldrich syndrome, hereditary retinoblastoma and a number of diseases characterized by human male infertility.

A very interesting preliminary survey of X-ray sensitivity has been undertaken recently in more than 50 different cell strains including representatives from normal individuals as well as from patients suffering from some of the possible DNA repair syndromes discussed above. An overall range of D_0 values of 38-180 rads was found indicating a considerable variability. The normal sensitivity was described by a mean D_0 value of 126 ± 17 rads. Six XP together with two cell strains from Cockayne's syndrome (all known to be sensitive to UV) fell into the normal range indicating an absence of cross sensitivity between UV and γ irradiation. All ten AT cell strains tested proved radiosensitive and gave a mean D_0 value of 57 ± 15 rads strongly suggesting that cellular sensitivity might be taken as diagnostic for AT. Representative cell strains from familial retinoblastoma, Fanconi's anaemia and Hutchinson-Gilford progeria occupied positions of intermediate sensitivity. These results also emphasize the importance of investigating a representative selection of cell strains for any one condition.

Cells from patients suffering from Fanconi's anaemia show extreme sensitivity to the bifunctional cross-linking agent, mitomycin C. It has been proposed that these cells lack an endonuclease specific for cross-linked DNA.

The relationship of DNA repair with chromosome aberrations and sister chromatid exchange has been explored in a number of these syndromes. In particular, lymphocytes, and to a lesser extent fibroblasts cultured from individuals suffering from Bloom's syndrome, exhibit unusually high levels of chromosomal aberrations and sister chromatid exchange. Studies of the latter phenomenon have been greatly aided by the discovery of "harlequin" differential staining techniques which distinguish between sister chromatids and can reveal SCEs. BS cells are normally competent in excision repair, postreplication repair and single strand break joining.

The distribution and types of chromosome aberrations present in BS cells are strikingly similar to those produced by mitomycin C, suggesting that BS cells can themselves produce a similar DNA damaging response.

Cells from some of these diseases have been assayed for the presence of the DNA polymerases α , β and γ ; in particular AT, BS, Fanconi's anemia, Progeria and Werner syndrome. The three enzymes are present at normal levels. In general, little progress has been achieved with regard to the detailed enzymology of repair in man. A brief review of the situation is provided in paragraph 2.1.3.2. (below) which is devoted to work on experimental animals.

2.1.3.2. Other vertebrates

Very important results (presented in detail in the document for discussion at Gif) have been obtained with other vertebrates which rendered possible the characterization of repair systems in mammals, the exploration of repair processes in germinal cell lines and the demonstration of relationships between DNA repair and chromosomal aberrations.

Direct experimental evidence of a link between defective DNA repair and malignant transformation has been made available through studies of pyrimidine dimers in the fish Poecelia. This fish has an efficient enzymatic photoreactivation and fish injected with a suspension of UV-irradiated cells prepared from members of their clone develop thyroid carcinomas in 100 % of cases. If, however, this cell suspension was treated, before injection, with photoreactivating light, a ten-fold reduction in the incidence of thyroid carcinomas was observed. Since the photoreactivation treatment should have specifically repaired at least part of the pyrimidine dimers produced by UV light, its effect on the incidence of tumours can be taken as evidence that pyrimidine dimers are important in malignant transformation.

Considerable advances have also been made in the localisation of human genes involved in repair. Hybrids, isolated after fusion of human and Chinese Hamster cells, specifically lose human chromosomes during culture. This means that hybrids can be isolated which have lost the genetic information for a part of, or for the whole human-excision repair system. By correlating the loss in

human repair-capacity with the disappearance of certain human chromosomes, repair genes may be localized. The human chromosomes lost can be identified by the disappearance of specific gene products recognized by marker electrophoresis supplemented by microscopic chromosome analysis and repair replication is measured after UV-irradiation. Studies using such hybrids for the localisation of DNA repair genes are in progress.

In addition, cell fusion techniques have been successfully used for examining DNA repair mechanisms. In one series of experiments human and chick fibroblasts were fused to give multinucleate human/chick heterokaryons after prior treatment of one of other parent strain with UV. The primary human cells lacked photoenzymatic repair but possessed excision repair whereas chick fibroblasts showed photoenzymatic repair but no excision repair. Experimental conditions were selected so that UV-induced damage resided only in DNA foreign to the repair enzymes under study. Repair machinery remained functional and was able to operate in heterokaryons so that repair enzymes coded for by either fusion partner removed dimer-containing sites from the DNA of the other with an efficiency comparable to that occurring in parental, unfused cells.

The occurrence of UDS in heterokaryons synthesized between XP and chicken erythrocyte cells has been demonstrated. Repair replication measured in different heterokaryons showing altered ratios of XP and chicken nuclei indicated that the UDS level found in XP nuclei was dependent on the number of chicken erythrocyte nuclei in the heterokaryon. UDS activity increased as the number of chicken nuclei increased. These results could suggest that the repair found in the XP nuclei was of the chicken type (i.e. no excision of thymine dimers).

In opposition to such refined analyses, the enzymology of repair in man and in higher eukaryotes has not progressed very rapidly. So far, only studies of easily available enzymes and substrates have been made. Excision repair in mammalian cells seems to have the same main features as in lower organisms. It seems likely that both base-excision and nucleotide-excision modes exist and enzymes capable of initiating the two pathways, namely DNA-glycosylases and specific endonucleases, have been found in animal tissues. Although a number of endo- and exonucleases have been isolated from mammalian cells, it is not clear which of these are actually involved in repair processes.

It is also uncertain which of the two types of DNA polymerases from mammalian cells normally carry out DNA synthesis for repair. The levels of the α enzymes increase during cell proliferation and may be primarily involved in the replication of DNA. In contrast, the β polymerase present in body tissues at an almost constant level is the proposed candidate in the processes of repair. Little, however, is known about a possible functional interchangeability of the two enzymes. None of the mammalian polymerases in their purified state possesses a "proof-reading" activity which may remove incorrect nucleotides occasionally inserted in newly synthesized DNA. The activities of DNA polymerase and of 3'-5' exonuclease were however found to be closely associated in enzyme preparation and they remained together through several purification stages suggesting that they could act together as an 'error-correcting' enzyme.

Isolated enzymes from calf thymus have been used to elucidate the mechanisms by which ligase seals radiation nicks in DNA. The enzyme rejoins DNA strand breaks that carry juxtaposed 3'-OH and 5'-PO₄ termini, whether or not the adjoining bases are correctly paired. Then, when acting directly on X-irradiated DNA, the enzyme restores the physical continuity of the double helix but may thereby fix premutational lesions in the genetic material. Because the ATP-dependent mammalian ligase has a lower specificity for the structural integrity of the DNA substrate than the NAD⁺-dependent enzyme from prokaryotes, it may well be that misrepair during ligation is more frequent than in lower organisms.

2.1.3.3. Insects

In recent years, many repair deficient mutants have been isolated in Drosophila, an organism which has been well-studied from genetic and radiobiological points of view. The repair deficient mutants have been isolated from wild populations and have also been induced in the laboratory. In some cases the mutants have been identified by direct screening for mutagen sensitivity while in others they have been identified as causing meiotic anomalies. Disturbances of meiosis, mitosis, enhanced rates of spontaneous chromosome breakage and mutation often coincide with enhanced radiation sensitivity. In vivo and in vitro studies can be carried out, and

it has been shown that there are several interlinked repair pathways, including excision repair and post-replication repair. Most of the mutants are located on the X-chromosome and seven complementation groups have been identified on this chromosome. Some autosomal mutants are also known to affect repair. Alleles of mei-9 and mei-41 enhance the radiation sensitivity of carriers and it has been shown that mei-9 in females affects the repair of damage induced by X-irradiation of sperm in non-mutant males.

2.2. Identification of important problems and possible approaches

2.2.1. Work with prokaryotes

It is difficult, in a field where basic problems are tackled and in which new developments have come to be more of a rule than an exception to establish clear priorities for a five year programme.

Up to now, the analysis of the mechanisms of the fate of DNA damage in human cells has always been aided by preceding discoveries made in bacteria. The use of bacteria has provided virtually every new concept subsequently used in research on radiation effects, mutagenesis and the molecular basis of cancer causation in mammalian systems. It has also provided new tools, for example, precise identification of DNA damage and its repair, and enzymes and pathways of repair. Furthermore, bacteria are the most likely hosts for the study of cloned mammalian genes, notably those involved in repair and carcinogenesis. Thus, research on prokaryotes are still rate-limiting for further advancement in mammalian systems.

The relationship between research with bacteria and research directly conducted on man may be modified in the future, now that detailed investigations can be carried out directly on human cell cultures and that the molecular biology of man has become a reality. Yet, prokaryotes and particularly E. coli, have a significant contribution to make in those areas where mammalian systems still display difficulties for precise analyses, that is to say with regard to :

- the identification of repair enzyme deficiencies in mutants;
- the determination of biochemical pathways of repair together with detailed enzymological studies.

It is thus along these two lines of research in particular, rather than upon the detailed inventory of genetic variants, that high quality research on prokaryotes should be stimulated and supported with the objective of providing new methods and techniques for the direct analysis of sensitivity and repair in human cells.

At the same time, in view of the recent discoveries on the effects of protease inhibitors in bacteria and mammalian cells and of the probable relationship between mutagenesis, inducible error prone repair and malignancy, the use of bacterial and viral systems together with that of appropriate mammalian cell lines, should be encouraged for characterizing the metabolic pathways involved in error prone repair, the promotion of carcinogenesis and for selecting efficient inhibitors.

Finally, and until suitable and reliable mammalian cell systems for screening and detection are developed, the use of bacterial tests for defining interactions between radiation and chemicals and for the standard evaluation of mutagenicity should continue to be encouraged.

2.2.2. Work with lower eukaryotes

Yeast is a model eukaryote combining some of the features of prokaryotes with unique characteristics for the study of processes and systems typical of all eukaryotes including man. It should be used to fill-in existing gaps between the radiobiology of bacteria and that of mammalian cells, in those specific cases where neither bacteria nor mammalian cells can be studied efficiently for solving basic problems considered of relevance to radioprotection. Such cases, among which certain concern other sub-sectors of the programme not always taken up in the outline of programme for the sub-sector on the genetics and biochemistry of sensitivity and repair, include :

Sensitivity to radiation and repair during meiosis

Radiobiological research in bacteria and in mammalian cells in tissue culture provides data only on those genetic events and repair mechanisms which take place during mitotic cell division. However, risk estimates of radiation damage in mammals require an understanding of the processes of genetic change and repair during meiotic cell

division and gamete formation. Some understanding of the events which take place after radiation damage of meiotically dividing cells may be provided by the use of diploid yeast cultures undergoing sporulation under controlled conditions. New information on radiation damage is likely to be obtained in a way not yet possible in the mammal if yeast cells are studied in both meiosis and mitosis. In this respect the numerous cell cycle (cdc) mutants and the dozens of radiation-sensitive (RAD) mutants presently available and partly characterized are unique assets. Also, the possibility of measuring the kinetics of formation and repair of double strand DNA breaks induced by low doses of ionizing radiation is at present unique in yeast.

Radiation damage and repair of mitochondrial DNA

So far repair of mitochondrial DNA after exposure to radiation has received very little attention and the mechanisms of recovery from the damage caused by ionizing radiation are completely unknown. Yet the understanding of repair mechanisms in mitochondrial DNA is of importance because in all eukaryotes, including human cells, mitochondria contain their own DNA encoding for certain polypeptides of the mitochondrial inner membrane. This genetic information is essential for survival of all human cells since it controls the vital function of respiration. Therefore repair mechanisms ensuring the fidelity of the information encoded in this DNA must exist. Yeast is the organism of choice to perform such study. Nuclear mutants can be easily isolated and thoroughly characterized genetically, especially those conferring radiation sensitivity (Rad mutants). On the other hand, yeast is the only eukaryote which can develop exclusively from glycolysis in the absence of functional mitochondria. It is therefore possible to alter the mitochondrion (radiations, nuclear and mitochondrial mutants, etc) and study the impact of the damage. In this respect, the recently discovered mutants modified specifically in the repair of UV damage of mitochondrial DNA and the mutants sensitive to γ -rays which are specifically modified in the mutability of mitochondrial DNA will be particularly useful. Moreover, the possibility of measuring the kinetics of double-strand breaks in mitochondrial DNA and also the possible existence of an inducible repair mechanism in mitochondrial DNA are particularly interesting and must be further explored.

Genetic manipulation

Protoplast fusion between yeast and higher cells is now possible. In addition, it has been recently demonstrated that yeast genes can be inserted and expressed in Escherichia coli and that bacterial genes can be cloned in yeast. These new and exciting technical possibilities should be exploited in radiobiology by genetic manipulation of the radiation-sensitive bacterial and yeast genes.

Radiation-induced repair

Recent indications of the existence of a radiation-induced repair system of yeast nuclear DNA open a new avenue which should be exploited and where the panoply of Rad and cdc mutants could provide new insights into the functions of SOS repair, and particularly the role of chromatin, which may then be exploited in mammalian cells.

Biochemistry of repair

Because of its availability in large quantities, yeast is appropriate for the study of the different enzymes of the different repair mechanisms. However not much work has been carried out in this respect and the enzymatic deficiency of only one of the 100 rad and cell cycle mutants has been identified so far (DNA ligase in cdc 9). It is thus presumably from bacteria rather than from yeast that short term developments are to be expected and should be encouraged. In the long term, however, yeast is likely to yield important results which can be more easily extrapolated to man.

2.2.3. Work with multicellular eukaryotes

It is probably in this area of the sector that most important break-throughs can be expected. An outline is given below of the material now available for analysis and of the approaches which should be made for establishing the molecular bases of radiation protection.

2.2.3.1. Materials of study

Human cell mutants

For experiments on the repair of damaged DNA within the framework of a radioprotection programme, the material of choice consists of human cells suspected to have an increased sensitivity to radiation. These cells are unable to cope with certain types of damage induced in DNA by physical or chemical agents. Generally, such cells come from individuals with inherited defects of DNA repair.

It appears feasible also to select cultured human cells that were originally normal but have acquired radiosensitivity either spontaneously or through induced mutations. However such a possibility has not yet been realized.

Special animal cells

Animal cells with special features of DNA repair are convenient tools for investigations. Of these, main examples are :

- Cell lines from Chinese hamster that do not remove pyrimidine dimers efficiently from UV-irradiated DNA but do repair UV-lesions other than dimers. Induced mutants with altered radiosensitivity are easily obtained from such rodent cell lines and extend the range of available repair-defective material.
- Chicken cells defective in excision repair but endowed with an active photo-reactivating enzyme.
- Marsupial cells which also have high levels of photo-reactivating enzymes. The use of cells from Drosophila is also of interest. Besides humans, this is the only animal species in which radio-sensitive mutant strains have been described and characterized genetically and biochemically.

Mammalian tissues

Tissues and organs from mammals or from human placenta are convenient starting materials for large scale purifications of enzymes acting in DNA repair. These sources can provide the quantities of purified enzymes that are needed for detailed biochemical studies.

2.2.3.2. Genetic analysis

- Complementation test by cell fusion

In the last ten years, somatic cell hybridization has provided complementation tests for the genetic analysis of mammalian cells. For studies in the area of DNA repair, one fuses two different mutant strains and usually scores for unscheduled DNA synthesis. These tests serve to differentiate between variants within the same repair pathway, but do not yield much information on the nature of the defective cell function.

- Gene mapping methods

Other methods of gene transfer that permit the mapping of genes on human chromosomes are also useful in DNA repair investigations. Such techniques are : the fusion of human and animal cells with gradual elimination of the human chromosomes from the hybrid, isolation of a few or even single human chromosomes and their introduction in mini-cells, formation of nucleus-cytoplasm hybrids (cybrids).

- Heterogeneous genetic systems

Heterogeneous cell systems with independent or combined expression of different genomes can be exploited for characterizing DNA repair variants. These systems include teratomas, chimeric mice and hybridomas. Methods using of recombinant DNA are presently unsuitable for research on DNA repair with animal and human cells. However, future developments in this area are expected. It seems advisable to search for DNA repair genes coded by viruses. Apparently, genes of this type are present in Herpes. Genetic characterization of viruses is now possible and the introduction of viral genes into the genome of mammalian cells in culture may facilitate genetic analysis of the host cell complement.

2.2.3.3. Biochemical analysis

- Biochemistry of DNA repair

The biochemistry of DNA repair in animal cells is mainly directed towards the description of the various repair pathways and the

identification of the enzymes involved. There have recently been some major advances towards these goals, but other lines of study have proven less successful. There is thus a requirement for new ideas and approaches. Data collected from bacterial systems provide a general framework for investigations in mammalian cells, but many differences in important details of the repair processes have been discovered.

Enzymology

A complete description of a biochemical pathway requires the isolation and characterization of the enzymes involved. A number of enzymes presumed to be involved in repair have been studied. However, the physiological levels of these enzymes vary greatly in different "normal" individuals making it difficult to prove unambiguously that a particular enzyme deficiency is associated with a particular repair defect. There is a need for a search for new enzymes which may be involved in repair pathways.

DNA repair in cells

Defects in DNA repair have been discovered in the UV-sensitive Xeroderma pigmentosum, but studies on the ionizing radiation-sensitive diseases have been much less successful. Techniques of improved resolution and new approaches are required in order to study minor pathways and residual unrepaired damage. The latter may be only a very small fraction of the initial damage. The use of antibodies against specific types of DNA damage may offer a sensitive way of studying the repair of particular lesions.

Studies on chromatin

In contrast to the DNA in procaryotic cells, chromosomal DNA in eukaryotes is associated with proteins in the nucleosomal structure. In some Xeroderma pigmentosum cell strains the defect seems to be specifically related to the ability to recognize damage in DNA packaged in chromatin. Studies on the nature of the DNA-protein interactions in chromatin and possible effects of DNA damage on chromatin structure should be encouraged.

.Artificial systems

A bridge between enzymology and whole cell studies is offered by the use of a number of artificial biochemical systems, e.g. (a) permeabilized cells, (b) cells injected with macromolecules or organelles by micromanipulation, (c) subcellular systems (isolated nuclei, chromatin etc.), (d) introduction of microbial enzymes into mammalian cells by the Sendai virus technique, (e) the introduction of cloned DNA repair genes from microorganisms, (f) production of antibodies against enzymes of DNA repair and their use as intracellular probes, (g) viruses can be utilized to detect cells deficient in DNA repair. For example UV-irradiated virus (Herpes, Adenovirus, SV40) will grow in normal but not in Xeroderma cells.

.Other cell types

Observations on cells other than fibroblasts and common cell lines (e.g. differentiated cells and germ line cells) should be encouraged.

2.2.3.4. Biological consequences

The most important radiobiological parameters are:

- . Decreased survival. This can be studied at the level of cells or organisms.
- . Mutagenesis. The relationship of DNA repair to mutagenesis can be studied in the human disease syndromes. It has not yet been definitely established whether error-prone repair pathways exist in mammalian cells. Only a very limited number of mutation assay systems are available, and the majority of the experiments use the hypoxanthine guanine phosphoribosyl transferase system. There is an urgent need for more assay systems to be studied.
- . Chromosome aberrations. Most reports of chromosomal aberrations in irradiated cells deal with formation of rings and dicentrics. These anomalies are cytogenetically unstable, i.e., they are not retained by the cells. The simple scoring of rings and dicentrics will result in an underestimate of induced chromosomal rearrangements.

Otherwise, translocations seem to be stable changes and represent an adequate index quantifying radiation effects on chromosomes.

The cause of the progressive disappearance of rings and dicentrics from the metaphase specimens is not understood. It is not yet clear whether the cells can restore the correct chromosomal structure or do not recover from the lesion, and lose with time the ability to enter mitosis. In the latter case the affected cells are gradually eliminated from the cytological screening.

It will be of interest to define whether the apparently reversible chromosomal alterations undergo repair and what are the relationships of these processes with the mechanisms repairing the various types of damage in the DNA molecules.

- . Sister chromatid exchange (SCE). The measurement of SCEs is relatively simple. The results can be related both to molecular processes and to other biological end-points.
- . Transformation. Attempts to produce morphological transformation in human cells have been largely unsuccessful. Possibly fibroblasts are not the right cell type in these experiments especially since the majority of human cancers are of epithelial origin.
- . Carcinogenesis
- . Premature ageing reduced life span
- . Altered gene expression. The association of radiosensitive human syndromes with defects in the neurological and immunological systems, may indicate that altered gene expression could be a consequence of DNA damage.

2.2.3.5. Screening assays for radioprotection : detection of individuals at high risks

A major goal of radiobiological investigations for protective purposes is the standardization of methods to define the normal range of radiation sensitivity in humans. Quantitative or reliable semiquantitative assays are required for selecting individuals that are at high risk among the professional workers on nuclear plants and in the general population.

Hopefully, the tests should be carried out at the cellular level and should consist of non-laborious, easily reproducible, short-term experiments. The following approaches are available :

- . Identification of heterozygotes of the radiosensitive syndromes. Heterozygous individuals for the genes implicated in the recessive congenital disorders of DNA repair are reasonably expected to display subclinical symptoms and to possess less efficient biochemical mechanisms for removing DNA damage (see also p. 324).
- . Test for cell survival. Though this can now be carried out on a routine basis in a well-equipped laboratory, these experiments are still too costly and time-consuming for general screening purposes.
- . Mutagenesis. These experiments are at present even more laborious. It is to be hoped that future developments may overcome some of these technical problems.
- . Chromosomal aberrations in blood cells. Such cytological tests need to be critically evaluated but are the only ones that can be applied for mass screening at present.
- . Sister chromatid exchanges. These can be easily scored in stimulated lymphocytes, but their significance needs to be evaluated.
- . DNA repair. A rapid DNA repair test would provide an ideal assay. However such a test would obviously only detect defects in the particular repair pathway under study. It is doubtful whether any of the existing techniques would have the required sensitivity, resolution or broad specificity.

The importance of this problem can be seen in relation to ataxia telangiectasia, where the homozygote frequency is of the order of 10^{-4} . The heterozygotes comprise 1-2 % of the population at large, and may represent a very significant "high risk" group of individuals.

Refined methods of genetic and biochemical analyses for DNA repair in human somatic cells should be devised for recognizing the healthy carriers of the radiosensitive syndromes. These assays should lend themselves to standardization for mass screening operations in groups of professionally exposed individuals.

2.3. Outline of programme for the sub-sector dealing with the biochemistry and genetics of radiosensitivity and repair

As a consequent of the elucidation, now well in progress, of DNA repair pathways in microorganisms, research involving the use of human cells having mutations leading to repair deficiencies has shown that the mechanisms for repairing DNA damage are of great relevance to human health. Several specific factors affect repair capacities and a number of hereditary diseases that are accompanied by an increased sensitivity to radiation and incidence of cancer are associated with defects in DNA repair.

A large part of the envisaged research is to be executed on mammalian, and particularly human, systems but the use of non-mammalian material will be necessary for the analysis in depth and the modelling of complex biochemical and genetical mechanisms.

The programme will include :

- a) surveys of the radiosensitivity of a variety of human cells (fibroblasts, lymphocytes, etc...) taken from normal "control" groups as well as from representatives of those human diseases showing enhanced sensitivity to environmental mutagens. Whenever possible, a detailed analysis of variations in radiosensitivity between individuals will be undertaken;
- b) identification and genetical and biochemical characterization of variant mammalian cell strains of differing sensitivity and deficient in repair of DNA damage;
- c) investigation of the detailed enzymology of DNA repair pathways (this is best studied at present in microorganisms where formal biochemistry and genetics are well established) and studies of the biochemical specificity and biological significance of DNA lesions in mammalian systems. This will include the use of proteins that recognize specific lesions as analytical probes for monitoring enzymatic repair and the relationship of lesions to mutation, recombination and chromosome aberrations;
- d) studies of mutagenesis and the role of constitutive and inducible repair pathways in mammalian cells. Use will also be made, in this

part of the programme, of the several DNA repair deficient mutants recently isolated in Drosophila which provide an opportunity for studying the role of DNA repair pathways in the realization of radiation induced genetic damage in an eukaryotic model system;

- e) analysis of the relationships of DNA repair and related mechanisms to carcinogens.

3. Sub-sector on the assessment and analysis of genetic damage in eukaryotes

The gene mutations and chromosome aberrations which occur spontaneously in man are a source of considerable hardship, being responsible for a substantial fraction of all spontaneous miscarriages and, in full-term survivors, congenital malformations, mental and physical disorders. The incidence of naturally occurring defects and diseases in human populations has been calculated by UNSCEAR to be approximately 1.0 per cent for dominant and X-linked diseases, 0.1 per cent for recessive diseases, 0.4 per cent for chromosomal diseases and 9.0 per cent for congenital malformations, multi-factorial and irregularly inherited conditions. It is thus particularly important, in view of the fact that irradiation is known to induce mutations and chromosomal anomalies (see Table 2 and Table 3), to improve as much as possible the present methods of detection of genetic radiation effects and to establish, through an analysis of the mechanisms of induction, the role of various factors and circumstances which may contribute to an enhancement of incidence rates.

For obvious reasons, such studies cannot, in the majority of cases, be carried out directly in man and have to be conducted on appropriate experimental systems which lend themselves to detailed cytogenetic and genetic analyses.

In this section, reference is first made to detailed reviews of the present state of knowledge which have been prepared for the Commission and by the Commission and which will be available upon request, as specific scientific documentation, before the initiation of the present programme. References to these two reports are followed by a chapter on the identification of important problems and possible approaches. The section ends with the outline of the Commission programme for this sub-sector on the assessment and analysis of genetic damage in eukaryotes.

3.1. Present state of knowledge

A detailed appraisal of the nature of radio-induced damage (mutations, structural aberrations of chromosomes, recombination and aneuploidy) in man and in multicellular organisms will be made available through the report by Dr. Sankaranarayanan under sub-contract 010 N 099-76-1 PSAF of the contract between the Community and the Commissariat à l'Energie Atomique. For each class of damage, this report follows the same analytical approach, namely :

Mechanisms

Observed frequencies in man

- sampling and scoring methods
- spontaneous rates and dose-response relations
- modifications of dose-effects relations
- effects and transmission
- problems and objectives for future research

Contribution from work with experimental species

- test systems available
- rates of occurrence
- dose-mutation responses
- effects and transmission
- extrapolation to man

With regard to the particular problems dealing with the nature and detection of chromosomal non-disjunction a detailed survey of the present state of knowledge is to be found in the Proceedings of a C.E.C. meeting on the radiation-induction of non-disjunction published by ELSEVIER as a special issue of Mutation Research (Radiation-induced non-disjunction, 61, 1 : 1-119, 1979). The proceedings include an inventory of the situation in man and a review of current efforts on a wide range of different test systems (Aspergillus, yeast, Drosophila, mice, Microtus, plants and human tissues).

3.2. Identification of important problems and possible approaches

A review was made, at the Brussels meeting in November 1978, of the research efforts which should be given priority for improving

the detection and the understanding of the three types of anomalies (non-disjunction, translocations and small deletions) which are of primary concern for the radioprotection of man.

Some of the main lines of reasoning and of the conclusions reached at this meeting and elsewhere through discussion with experts, are presented below :

3.2.1. Non-disjunction

At present, we are dealing with the purely descriptive situation of a phenomenon with a high frequency of incidence. It is necessary, for working out the kinetics of radiation-induced non-disjunction to identify the targets and to understand the mechanisms. The analysis of dose-response curves in experimental material may provide information on targets. With regard to mechanisms, one approach could be an analysis of relationship to repair which may render possible the isolation of the various components leading to non-disjunction. Drosophila stocks deficient in various repair capacities are now becoming available and can be used for this. At the same time, attempts should be made in other eukaryotes, and particularly in mice, to understand the processes through which irradiation induces missegregations of entire chromosomes and chromatids.

However, the importance of epidemiological surveys should not be underestimated. Testicular biopsies are available (from patients with cancer) which allow the study of spermatogenesis after irradiation treatment. Some biopsies are also available for analysis on the female side. Collaborations should be established with clinicians.

Concerning the analysis of the cytogenetic factors influencing non-disjunction, the study of the relationship between satellite associations and the occurrence of aneuploidy should not be given a very high priority unless new elements are available which clearly demonstrate a relationship. The work should probably be carried out, at any rate, in test systems available in experimental species. Similarly, in view of the lack of evidence for any causal relation, only limited attention should be given to the role of heterochromatin on non-disjunction. Some exploratory work should be carried out,

however, in Microtus and through the incorporation of heterochromatin on chromosome 13 of mouse because recent reports suggest that polymorphism of constitutive heterochromatin has some bearing on the incidence of Down's syndrome. In contrast, high priority should be given to investigations dealing with the direct analysis in man of irradiation effects on the synaptonemal complex which is likely to reveal intermediate events leading to non-disjunction (absence of recombination nodules, interlocks ...).

3.2.2. Other chromosome anomalies and point mutations

The possible involvement of sister-chromatid exchange (SCE) and/or mitotic recombination as an essential step in tumour promotion or, at any rate, its inducibility by tumour promoters such as TPA, justifies a stimulation of research efforts on the analysis of the mechanism involved and of the conditions leading to SCE in irradiated cells. Studies of relationships between SCE, mitotic recombination, mutagenesis and carcinogenesis should continue.

With regard to translocations, there is a need to accumulate more information on reciprocal translocations and to analyse the occurrence of Robertsonian translocations in the female side. Mouse, in spite of certain disadvantages (the dictyate stage is reported by some to be very different from that of man, chromosomes are normally acrocentric and extrapolation is difficult) should be used as test material because reciprocal translocations occur frequently and because strains with metacentrics are now available. At the same time, however, one should collect more human data for working out a basis for extrapolation and use should be made, in this connection, and whenever possible, of exposed human testes.

Utilization of Neurospora endonuclease, as recently used in Leiden, for probing the primary events leading to aberrations is recommended in all cases where it is likely to shed light on specific questions related to the formation of chromosomal anomalies.

For the determination of factors influencing the occurrence and rearrangement of breaks, one should consider arm length, heterochromatin and repair. The relationship of heterochromatin to rearrangement

may at first sight appear less critical because breaks in heterochromatin do not rejoin with those in euchromatin. Yet, several pieces of euchromatin are inserted in heterochromatin. The relationship of repair to the type of aberrations produced should be studied in man, where several homozygous and heterozygous repair deficient lines are now available (Ataxia, Xeroderma...), using modern banding techniques and systematic approaches similar to those carried out by EMERIT and others with diffuse and systemic xeroderma. Similar research is also possible with Drosophila as more and more repair deficient strains become available.

With regard to small deficiencies, which may constitute the basis of specific locus mutations in eukaryotes, there is a need to establish the mechanism of induction involved. Spermatogonia yield a linear response with protracted irradiation but the relationship is unclear with acute irradiation. In the case of oogonia, this relationship is quadratic.

Is there any such thing as point mutations induced by radiation in Eukaryotes ? Except for yeast (cytochrome C) where single amino acid changes can clearly be detected, the evidence is lacking. Isoelectric focussing techniques do not appear successful but nucleotide sequencing should soon become possible with the aid of restriction enzymes. Work should be supported for characterizing in detail the types of mutations induced in man.

3.2.3. Associations between radiosensitivity, repair and segregational anomalies

Meiotic mutants are now becoming available in eukaryotes which will allow the analysis of these associations. They are numerous in yeast where, unfortunately, very little is known on non-disjunction. In Drosophila, excision repair deficient lines and post-replication repair deficient lines have been selected for a very high rate of spontaneous non-disjunction. They should be studied extensively.

3.2.4. Interactions and relationships between the biological effects of radiations and other environmental agents

No clear selection has yet been made of the environmental agents which should be considered in studies of this kind. Harman and non-Harman substances, inhibitors of tumor promotion (such as antipain or leupeptin which inhibit formation of TPA induced SCE), hormones, pollutants, electrophilic substances including radio-sensitizers used in therapy, modifiers of the secondary structures of DNA can be suggested but limitations in funding possibilities obviously require that only a few selected agents be considered in the programme for detailed research on interactions.

3.3. Outline of programme for the sub-sector on the assessment and analysis of genetic damages in eukaryotes

Since human systems are usually not amenable to detailed genetic analyses, a substantial portion of the research effort will be carried out through the use of other eukaryotic material where the similarity of chromosomal organisation (DNA, histone ...) and of cellular organelles implies that many of the induction mechanisms for damage in the nucleus and in the cytoplasm are identical to those of man. The programme involves :

- a) the improvement and development of assay systems and experimental methods with increased resolving power for the detection of induced alterations in both somatic and germ cells of man;
- b) elucidation of the mechanism leading to chromosomal non-disjunction and other aberrations including studies of the relationship between chromosome structure and behaviour (heterochromatin, synaptonemal complex and satellite association);
- c) study of possible associations between radiosensitivity, repair and segregational anomalies;
- d) specific studies on the interactions and relationships between the biological effects of radiation and other environmental agents;
- e) elucidation, through a few selected studies, of the effects of irradiation on the mitochondrial genome and its implication for cellular survival.

4. Sub-sector on dose-effect relationship

Whereas the other two sub-sectors presented above are dealing, through the detailed analysis of mechanisms and of interactions, with the long-term establishment of a rational basis for the development of predictive and preventive methods in radioprotection, this third sub-sector is essentially devoted to the empirical assessment of dose-effect relationships in man or in species from which experimental data can be extrapolated to man. To achieve this, two methods of assessment (the direct method and the doubling dose method) are available which require the acquisition of knowledge on the increase by radiation of the frequency of hereditary effects and on the relationship with dose, dose-rate, LET and stage.

The state of knowledge presently available for the application of those methods is outlined below and is followed, immediately after, by an evaluation of pending problems and of possible approaches for reaching the objectives of the Commission programme.

4.1. Present state of knowledge

The evaluation of current knowledge which is given here only deals with the definition and use of assessment methods. This matter has been reviewed in January 1979 by a study group of experts who convened at Harwell upon a joint invitation of the Commission and of N.R.P.B. For a detailed inventory of scientific achievements in the field, reference is to be made to the report prepared for the Commission by Dr. Sankaranarayanan (sub-contract N° 010N-099-76-I PSA F) and to the relevant sections of the Proceedings of the meeting of C.E.C. contractants, November 78, Brussels (Mutation Research, Vol. 61, 1 : 1-119, 1979).

4.1.1. Direct method of assessing risks in human populations

In this method, the genetic damage induced by radiation in man is estimated directly from the result of radiation experiments on animals with some input from human genetics. This method involves several assumptions which have been described in the latest UNSCEAR report. Table 2 is derived from that report.

End-point	Expected rate of induction per million gametes resulting from irradiation of		Expression in first generation per million births
	Spermatogonia	Oocytes	
1. Autosomal mutations	60	-	20
2. Dominant visibles*	very low	-	
3. Skeletal mutations*	4	-	
4. Balanced reciprocal translocations ¹	17-87	low	low
5. Unbalanced products of end-point above	34-174	-	2-10
6. X-chromosome loss*	very low	low	low
7. Other chromosome anomalies	-	-	-

* mice

¹ man and marmoset

Table 2. Risk of induction of various kinds of genetic damage in man per 1 rad at low dose of low LET irradiation.

Disease classification	Effect of 1 rad per generation	
	first generation	equilibrium
Autosomal dominant and X-linked diseases	20	100
Recessive disease	relatively slight very slow increase	
Chromosomal diseases	38	40
Multifactorial diseases	5	45
Total	63	185
Percentage of current incidence	0.06	0.17

Table 3. Estimated effect of 1 rad per generation of low-dose, low-dose rate, low-LET irradiation on a population of one million live-born individuals assuming a doubling dose of 100 rad.

Estimates for recessive mutations are based mainly on recessive lethals in mice. It assumes that the rate of induction of recessive lethals reflects the genome rate for the induction of point mutations in general. Specific locus results are additionally used to gauge the magnitude of the dose-rate effect. These points are still open to question in the mouse and the estimates for man are even less certain.

Estimates for dominant mutations rely mainly on studies of skeletal mutations in mice. It is necessary to estimate what fraction of total dominant mutations affecting bodily systems will be found by studying the skeletal system. Further assumptions are required in considering what percentage of the mouse skeletal malformations could cause a serious handicap if induced in humans. Dominant mutations often exhibit irregular penetrance and applying mouse data to man in this context requires some caution. The chromosome mutation data are based on limited species involving human and marmoset spermatogonial irradiations. This is tentative and may need revision when more is known on the heterogeneity of primates. The transmission rate of balanced translocations to the F_1 is assumed to be one quarter of the frequency in spermatocytes. This is based on the known behaviour of translocation heterozygotes at meiosis. Post-meiotic selection against certain translocations may of course lead to lower rates.

The data are most inadequate for risk estimations of genetic damage induced in oocytes. From data in the mouse it is tentatively assumed to be low for humans but no quantitative estimates are possible.

4.1.2. Doubling dose method

In this method quantitative information is required on three factors :

- a) The natural incidence of hereditary disease. This is not known with certainty and present estimates rely on the work of Trimble et al in British Columbia with substantial modifications for the regular dominant diseases.
- b) The relationship between natural incidence and mutation rate.
This relationship is not well founded for dominants with reduced

penetrance or for the multifactorial diseases, although the latter constitute the largest component of hereditary disease in a human population. The frequency of some of these conditions is believed to be maintained by a selection mechanism. Thus an increase in the mutation rate may not influence greatly the prevalence of the conditions. However, it is still necessary to determine the extent to which the conditions are maintained by mutation and also their average persistence in terms of generations.

- c) The mean radiation dose necessary to double the mutation frequency. This is obtained from protracted exposures of mice and the value of 100 rads is taken to be representative of the many types of mutational events. The values given by UNSCEAR assuming a doubling dose of 100 rads are given in Table 3.

4.2. Identification of important problems and possible approaches

4.2.1. Assessment of risks in human populations

The needs and problems are to :

- characterize abortions which are well defined in time and about which some extrapolation may be made to the incidence of damages in lymphocytes at the time of exposure;
- define the populations which are to be screened;
- work out precise dosimetry;
- disentangle radiation effects from those of other mutagens (hair-dyes, chemicals ...).

Suitable groups are being sought in an attempt to make at least some assessment of risks. In Scandinavia, patients with testicular carcinoma who have received a genetic dose of 100-150 rad are being analysed. Approximately 100 biopsies are available. Abortion rates and incidence of anomalies are being estimated and it may be possible to relate to pregnancies. However, very few children are born and control material is difficult to find. Similar difficulties are reported in the United Kingdom in attempts to follow irradiated patients.

The work carried out at Edinburgh on the lymphocytes of dockyard workers showed that it is possible to detect chromosome aberrations at doses below the internationally agreed maximum permissible levels and it may be worthwhile to continue analyses on larger populations of exposed individuals and to associate such studies to enquiries on causes of death.

Several other groups could also be screened in the Community (women treated with therapeutic X-rays for congenital hip predislocation, people who suffered from TB, occupational workers, radiologists ...) but results in the past have been most discouraging. In the U.K. a National Registry for Radiation Workers has been set up. Doses received by workers each year will be recorded in the Registry and these doses will be correlated with causes and ages at death. It has been suggested that off-spring of radiation workers should be followed to ascertain whether hereditary effects are more frequent in these individuals than in the off-spring of non-radiation workers. The political and scientific difficulties in this type of study are numerous and very good co-operation from the radiation workers would be required. Nevertheless, registers should be harmonized throughout the entire community of Member States. Large scale screening may perhaps permit very sensitive individuals to be identified and to find what fractions of the populations are sensitive and at risk. A common action is now in progress with regard to the registration and the analysis at Community level of the incidence of congenital anomalies.

Is it worthwhile screening populations in areas of high natural radioactivity ? Work could be carried out at several different locations (Aberdeen, Central Alps, South of France ...) but such sites are not heavily populated and suitable control groups do not exist.

Alternatively one might approach the problem from the opposite end, starting with children having Down syndrome and checking the parents. Attempts made in this direction have been unsuccessful so far.

Finally, and as underlined on p. 312 , an attempt could be made, on the basis of the criteria listed in table 4, to screen sensitive

individuals or sensitive groups at risk. Except for clear cut cases of genetic diseases (table 5), for which there is an urgent need to define the radiosensitivity of apparently normal heterozygotes (who form 2 % of all human populations in the case of Ataxia and Xeroderma and still higher percentages if other diseases are considered), there is probably no such thing as isolated groups but, instead, a continuous spectrum for genetic variation in radio-sensitivity. This spectrum should be analysed.

Among environmental factors which sensitize to radiations, no cases appear to be known of groups subjected simultaneously to sensitizers and to radiation exposure. Differences in day and night rhythms which lead to variations in radio-sensitivity have been found in mice and may perhaps exist in man. They should be attributed to the consequences of synchronization by the day-night rhythm.

In conclusion, the best material for attempting to tackle this difficult problem of risk assessment in human populations consists of :

- radiation workers (most hopeful group but screening connected with political problems)
- treated patients
- sensitive groups, if these can be identified.

The genetic basis of most congenital malformations is so poorly understood that it would be desirable, if anything is to be done, to concentrate on specific and well defined genetic diseases.

4.2.2. Counselling

This is a practical problem which, in itself, does not require research. Decision on the information and advice to be given to exposed individuals is to be taken case by case. As a rule, exposed post-meiotic germ cells should not be allowed to reproduce and amniocentesis should be performed whenever possible.

With regard to the application of the doubling dose method, the Hiroshima and Nagasaki data have shown that an exposure to 100 rad

1. Inherited trait (genetic disease)
2. Sensitivity to ionizing rays (IR^S)
3. Sensitivity to sunlight and U.V. radiation (U.V.^S)
4. Cancer proneness
5. Chromosome instability
6. Premature aging
7. Immune and neurological disorders

Table 4. Criteria for defining repair mutants in man.

Xeroderma pigmentosum : composite syndrome consisting of 9 complementation groups with U.V.^S cells. One or two strains are also IR^S. Seven groups correspond to classical Xeroderma and 2 groups belong to a variant form with deficiency in post replication repair.

Ataxia teleangiectasia : Specifically IR^S and comprises 3 complementation groups.

Bloom's Syndrome : A "chromosome breakage" disorder with cells susceptible to DNA damage by ethyl m^ethanesulphonate. Probably associated with increased sensitivity of cells to the U.V. radiation at the lower end of the sunlight spectrum.

Progeria : Apparently IR^S syndrome.

Werner's syndrome : Similar to progeria; has been mainly reported as a IR^S defect.

Cockayne's syndrome : Very likely the cells are U.V.^S.

Familial Retinoblasma : A dominant IR^S trait.

Huntington Chorea : A dominant neurological disorder with IR^S cells.

Down's syndrome : In this well known disease, the cells seem to be IR^S at the chromosomal level with respect to the induction of chromosomal rearrangements.

Table 5. Human repair mutants (for more detailed descriptions, see p. 8-11).

leads to a 50 % risk and that the doubling dose corresponds to approximately 20 rad. However, it is impossible to make any decision if data are not available on the exact stage of the embryo which has been irradiated because differences in sensitivity between stages are much greater than expected. Information on all stages (and particularly pre-implantation stages) must be made available.

4.2.3. Social costs

Is it possible to establish an index of the severity of social costs for inherited conditions ? UNSCEAR built a system but gave it up in view of its complexity. Cost estimates are available for several disorders in most Member States but certain syndromes (XXY for instance which is predominantly male) have not been evaluated accurately. There is a need to follow up new borns with minor anomalies and to determine the meaning of such defects. Large surveys carried out at Edinburgh (involving 16.000 babies) permitted the detection of pseudo-normal Klinefelter's and Turner's syndrome patients very different from the typical case. Pseudo-normal carriers are rare in the case of autosomal anomalies but relatively abundant with regard to irregularities in the distribution of sex-chromosomes.

4.2.4. The kinetics of lymphocytes

Irradiation reduces the population of lymphocytes which, in the case of partial body exposure, always consists of irradiated and non irradiated cells; there is thus a need to estimate the situation after whole body exposure. At the moment, analyses after partial exposure always lead to an underestimate of the dose and the basic problems are :

- to find out the distribution of anomalies at any particular time in lymphocytes
- to establish their significance.

It is now possible to extract lymphocytes, to label them, to put them back and to establish distributions. One may also follow the blood situation in young people and, later on, their reproduction.

The problems arising from differences in sensitivity between B and T lymphocytes are solved now that the two types of cells can be separated at 99 % efficiency.

At Edinburgh, a good correlation has been obtained between data originating from irradiation of lymphocytes in vivo and in vitro. One should work out similar comparisons with testis biopsies but the difficulty is that the testes available for biopsies have usually been well shielded. Yet, 10-15 rad constitutes the critical dose and there may be sufficient leakage in the shielding for such a low exposure to occur.

An approach could be initiated in animals (pigs for instance), through extracorporeal irradiation, to establish an overall view of the problem and the precise determination of the type of research to be carried out with human material.

4.2.5. New assay systems and new detection methods

New methods, such as those of P. JACOBS, using hamster eggs for detecting non-disjunction and reciprocal translocations in human sperm, of LATT for measuring SCE and of STRAUSS and ALBERTINI should be tested and adapted to specific radioprotection problems. At the same time, and more simply, sperm counts, which have been carried out in mice, could be performed for man. However, information on the value of analyses of the morphology of human sperm is most contradictory. PROPESCU and LANCRAJAN, in Rumania, claimed that the motility and morphology of spermatozoa from humans exposed to low doses (2-20 rad) was significantly altered but preliminary work at Edinburgh and in the U.S.A. reveals 30 % abnormal sperm in normal men and an extremely high background noise from viral infection, allergy, hormone treatment, ... At Edinburgh, 4 or 5 major anomalies were found in 8 smokers out of 20 studied. In contrast, cases are known in France of individuals with chromosome anomalies who produce normal sperm. In addition, one may wonder if the sperm abnormalities observed have any genetic significance (haplontic selection).

As a general rule and whenever possible, full use should be made, for assessing damage to chromosomes in dose-effect analyses, of the

wide range of modern banding and labelling techniques now available for the identification of exchanges, breaks and rearrangements. It is generally believed that the application of such techniques may increase by a factor of 1-4 the number of aberrations which may normally be detected in irradiated cell samples using classical procedures.

4.2.6. Extrapolation from somatic to germ cells

There appears to be, for chromosomal aberrations, a relationship from somatic to germ cells of 4 : 1 in the mouse and 20 : 1 in the monkey. In order to establish the ratio for man, attempts should be made, at doses higher than 10 rad, to combine studies on somatic cells with testis biopsies. In spite of many problems (for instance, radiation blocks to spermatogenesis which induce a waiting period and render comparative work with spermatocytes difficult) there is a need to carry out work for relating data from lymphocytes to data from testis biopsies. The material is so scarce that a pooling of efforts through Community action is essential. Centralisation of analyses may be impossible but co-ordination should be established to stimulate at least the harmonization of methods and exchanges (information, slides ...). Similar efforts could be extended to other patients (Hodgkins, which involves chemotherapy and not radiotherapy and 30 : 1 fold differences in sensitivity, leukaemias...).

In the mouse, where data can be obtained for pigment cells and germ cells which do not reveal great differences in mutation frequencies, forward and reverse mutation test system should be developed for allowing precise comparisons in vivo.

Among the factors responsible for differences in sensitivity between somatic and germ cells, differences in repair activity and in cell cycles should be investigated.

In this area of research, more than in any other, there is a need to harmonize techniques and methods and to have the same group of scientists working on both the somatic and the germinal material.

4.2.7. Extrapolation from experimental species to man

The ABCW method and the arm number concept have proved to be invalid and therefore cannot be used for extrapolation. Three possible alternatives could be contemplated :

- arm length
- amount of repetitive DNA
- cell cycle time (this should be confined to the first cell cycle and the situation analysed in monkeys).

As a general rule, the experimental species used in animal studies should consist of :

- mammals with well defined genetic markers which could allow the analyses of complementation within gametes
- selected primates which provide, on the basis of their cytogenetic evolution and present karyotype, a suitable basis for extrapolation to man (cf. presentation made by Dr. DUTRILLAUX at Harwell and at Gif-sur-Yvette).

At the same time, attempts to apply the parallelogramme approach should be made by establishing, if possible, a firm relationship between the incidence of damage in peripheral blood and in testes and by finding out the ratio of translocations to point deletions.

At present, enormous differences in results can be observed between different laboratories (from 15 to 60 % of dicentrics have been recorded in identical samples in different institutes). Attempts should be made to harmonize methods.

Thyroid material from populations exposed to ¹³¹I is available. Analyses of metaphase plates could be carried out in combination with follow up studies in the populations and compared to data from animal studies.

4.2.8. Dose-effect relations in the rad range

As in the past programme, there is a need to work out dose response curves for different genetic end points after exposure to low doses and low dose -rates. Results obtained with available systems (Nicotiana, barley) should be confirmed and attempts should be made to develop accurate scoring methods for gene mutations and chromosomal anomalies in mammalian cells. The work carried out at Edinburgh on the lymphocytes of dockyard workers showed that it is possible to detect effects at the chromosome level below the internationally agreed maximum permissible levels.

4.3. Outline of programme for the sub-sector on dose-effects relationships

It is particularly difficult to establish the relationship between dose and effect in man because insufficient human data are available and because the quantitative extrapolation of experimental results to man poses serious problems. In view of the importance of dose-effect relationships for the assessment of radiation risk, the programme includes :

- a) epidemiological surveys which focus attention on the relationship between the dose received, the frequencies of aberrations in lymphocytes and the long term biological consequences of the exposure (aplasia in germinal cells and induced effects in live-born and still-born children),
- b) determination of the in vivo kinetics of lymphocytes with the view of facilitating the interpretation of doses from non-uniform exposures,
- c) investigations with mammalian experimental species (including primates when possible) designed to collect more data (genetic as well as cytogenetic) which will be useful for quantitative extrapolation of radiation genetic hazards to man,
- d) studies aimed at the appraisal of the methods and assumptions involved in risk assessment in extrapolating from somatic to germ cells and from experimental species to man,

- e) studies on the induction of mutations in germ cells and somatic cells at very low doses and dose-rates and the development of techniques to facilitate such studies.

EVALUATION OF RADIATION RISKS

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EVALUATION OF RADIATION RISKS

1. Significance of the subject.

Concepts used in radiation protection are liable to be applied in different ways in the Member States. For this reason, it is necessary to attempt to establish common methods for assessing as accurately and objectively as possible the consequences of irradiation for man and his environment. The results of such exercise are also needed for decision making on siting and on choices for energy supply. The new principles of optimization and limitation in radiation protection, which have been recommended in 1977 by ICRP, are based on a risk and detriment concept and require the assessment of realistic relationships between dosimetric quantities and genetic and carcinogenic risks. New dosimetric quantities and concepts have been developed; among them are the effective dose equivalent and the dose equivalent index for the description of individual exposure, and the collective dose and the collective dose commitment for the assessment of the collective health detriment. The practical application of these new terms has to be tested and their relationship to measurable quantities has to be determined.

2. Research areas

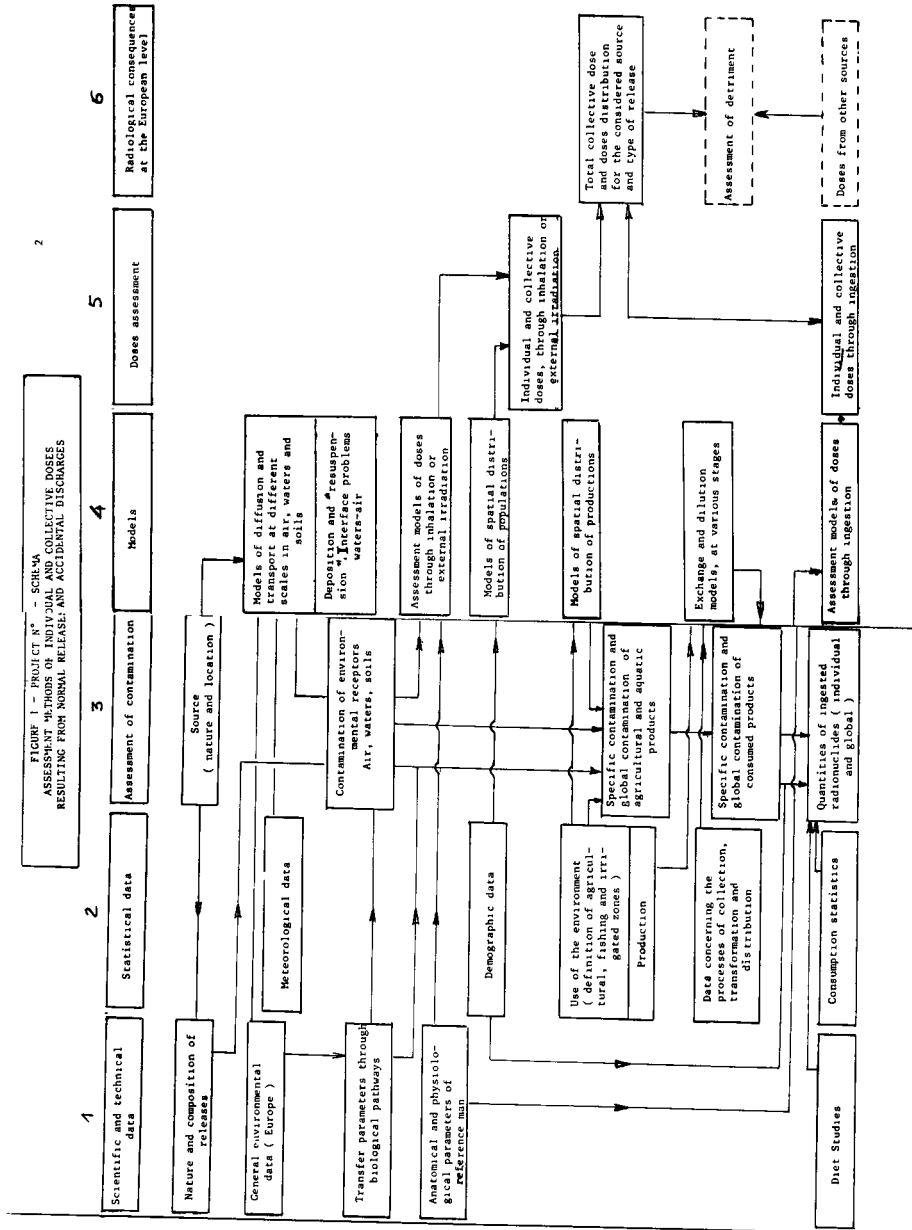
2.1. Methods for assessing individual and collective doses

The studies contributing to the assessment of individual and collective doses and of their distribution are summarized in the following scheme (Figure 1).

For the whole fuel cycle, they apply to the various types of releases : continuous, exceptional by concerted releases, accidental.

According to the physical form of releases and to the nature of the receptor, three conventional categories of problems can be distinguished :

- consequences of liquid releases in continental and marine waters
- consequences of atmospheric releases
- consequences of protracted releases from storage sites.



The assessment of collective doses requires taking into account long range transport of pollutants and of vectors of contamination reaching the populations directly or indirectly. This justifies the need for collecting statistical data, such as demographical data, and for developing new models (large scale diffusion in the physical environment, economic exchanges) aimed at completing the conventional models used for assessing individual doses. Models and data are to be adapted, as far as possible, to European conditions.

The problems involved have been grouped in the six columns of figure 1, and the links between them have been identified. They are:

- scientific and technical data
- statistical data
- assessment of environmental contamination and vectors of contamination
- models (physical, dosimetric, economic)
- assessment of doses
- assessment of radiological consequences on a European scale.

2.1.1. Most of the scientific and technical data (Column 1) are already available, but updating may be needed in certain cases, as well as complementary data on specific questions, allowing a choice of values fit for the use in European environmental conditions. The parameters of transfer of contaminants to aquatic products in continental and marine environments, and to irrigated productions, can be quoted as examples.

2.1.2. Many of the statistical data listed in Column 2 are presently available, but must still be completed in certain cases :

- the demographic data still must be completed for some countries
- the data for agricultural productions are available to a large extent,
- the gathering of data concerning the processes of collection, transformation and distribution has been completed for a few important products : cereals for France, sea products for the

French fishing zones, milk products for Europe, and bovine meat. Consumption statistics are analyzed simultaneously.

- the detailed meteorological data which are needed for long range assessments of the consequences of atmospheric releases have been collected and processed for the areas situated North of the 36th parallel.

These meteorological data bear on a one-year period. It will probably be necessary to gather data for other years.

- 2.1.3. The conventional models are grouped in Column 4, as are also those which concern more especially the assessment of collective doses.

The distribution models of populations on the one hand, and of productions on the other hand, have already been worked out and harmonized, as well as the exchange models.

The models for diffusion and transport on large-scale of pollutants still raise numerous problems.

- The atmospheric models have been given priority. The MESOS model has been worked out and its testing is in progress. Still, comparisons with other models and with available results of measurements have to be carried out in order to facilitate the choice of the models which have to be used in different practical cases (for instance, in applications of Article 37 of the Euratom Treaty).
- The models of diffusion in continental and marine waters should be further developed, particularly those dealing with long-range dispersion in the sea, which sets even more difficult problems than the atmospheric dispersion, and where simplified conventional hypotheses cannot be accepted as they stand.
- The interactions between marine, continental and atmospheric environments can play an important role. This has already been taken into account in the MESOS model as far as it concerns the influence of the nature of the crossed surfaces (land, sea) on the atmospheric dispersion, deposition and dilution of contaminant concentrations. In certain cases, "resuspension" should also be taken into account.

- The models for assessing the consequences of protracted radioactive releases from continental storage sites should also be further developed.

2.1.4. The development of the above mentioned methods will render possible the assessment, for every source under consideration, of the contamination levels (Column 3), and of the individual and collective doses and their statistical distribution, including mean levels, groups of various exposures and exposures as a function of time (Column 5). The results will have to be presented in an appropriately defined European grid model.

2.1.5. The resolution of the following problems (Column 6) :

- additivity of sources
- application of dose-effects relationships

leads to the assessment of the radiological detriment for populations (see paragraph 2.2. hereafter). Some cases should be worked out as examples, at European level.

2.2. Methods for assessing the detriment

The methodology of genetic, stochastic and non-stochastic detriment assessment should be developed along 2 convergent lines, namely

- exploitation of epidemiological studies which, through human population studies, should contribute to establishing dose-effect relationships in various natural or man-made situations,
- exploitation of experimental research data, intended to set-up experimental models of human radiation-induced diseases or deleterious effects.

Moreover, theoretical studies should be carried out in order to devise mathematical and conceptual models where experimental data are checked against epidemiological evidence.

Full use will be made of epidemiological and experimental data obtained in other sectors of the Radiation Protection Programme, and in research and syntheses carried out elsewhere.

2.2.1. Epidemiological studies play a central role in the assessment of detriment, and should follow three approaches.

The 1st approach covers long-term retrospective studies of people exposed decades ago to ionizing radiation for various medical reasons (case-control studies in most cases). These studies should try to determine whether there exists any synergism or interaction between irradiation and other factors of the environment.

The 2nd approach covers a major source of population exposure data, i.e. occupational exposure.

Cancer epidemics have been described earlier in miners of Schneeberg and Joachimstal who were exposed to radon and its radioactive daughter-products, and who also showed a high incidence of lung diseases such as pneumoconiosis and lung fibrosis.

By contrast, employees of nuclear industries have shown an excellent health record, making this industry one of the safest. However, questions have been raised recently on the existence of higher-than-expected risks for workers exposed to low doses of ionizing radiation. The data on which these assumptions are based were provided by case-control studies, and it is widely acknowledge that this type of data need to be checked and confirmed by other methods before they can be considered as valid. It is thus planned to set-up a European register for workers of the nuclear industries, or to coordinate - and possibly harmonize - existing national data collections in order to be able to conduct in a few years long-term incidence studies on numerous populations of the dose-effect relation at low doses. Cooperation with non-member states could prove useful in this respect.

Finally, a 3rd approach is the study of a possible relationship between natural radiation and some biological and medical problems in man. This approach should be followed cautiously, in view of contradictory findings in the literature and of preliminary observations confirming the complexity of the problem.

2.2.2. The quantification of results of experimental research on genetic, stochastic and non-stochastic effects, and their extrapolation to man, are also essential elements for detriment assessment.

Results of experimental research are to be treated through different evaluation methods. Those methods which most conveniently lead to assessing the cost of health effects (see 2.3.) should serve as guidelines for the deployment of experimental research whenever data are lacking for setting-up models of radiation-induced diseases or effects.

2.3. Assessment of economic and social consequences of irradiation

2.3.1. Studies already carried out have shown that the problem of assessing the economic and social consequences of irradiation must be seen in a more general frame, namely the development of rationalization methods for radioprotection choices. The assessment of the consequences of irradiation for populations is one of the stages leading to the development of cost-benefit methods. However, numerous quantitative alternative methods can be used for "optimizing" radioprotection, and they approach the problem of assessing consequences of irradiation from different angles. On the other hand, these various methods (cost-efficiency and multiattribute analysis, utility of functions, etc.) are not always necessarily based on the "optimum" concept. Therefore, it seems preferable to use the wording "rationalization methods for radioprotection choices" rather than "optimization methods". Studies performed up to now have mainly dealt with the exploration of rationalization methods in a decisional framework which was limited to the protection of the public and to the normal operation of the light water fuel cycle. The "cost-efficiency and "multiattribute" methods have been compared in this decisional context. This comparison has shown that both methods, used in a realistic way, lead to roughly identical results. However the multiattribute analysis is of particular interest because it allows a synthesis of the traditional individual approach and the collective approach. This feature should tend to ease the reservations of those who fear the consequences of an inconsidered use of the collective approach by showing that it leads in fact to make both conceptions of radioprotection complementarity.

2.3.2. The exploration programme of the decisional methods should be extended to the study of utility functions. Moreover, a comparison of the possibilities and limits of various methods must be performed. The aim of this exercise will be to assess the methods in respect to each other and to determine the hypotheses and constraints associated with each one. The comparison will focus on four main types of methods : cost-benefit, cost-efficiency, multiattribute and utility functions.

Most of these methods require an information which is necessary in order to assess the "ALARA" dose levels : it is the implicit value of the avoided health effect (or of the human life, or also of the man-rem).

Therefore, a search for implicit values of human life such as those resulting from earlier health protection practices in various industrial sectors (including the electro-nuclear field), must be developed, as much for the workers as for the public. This research, which will require an important phase of technico-economic data collecting, should provide a general set of variable values, which will allow the protection choices in the electro-nuclear field to be placed in relation to the choices made in other sectors.

Finally, case studies should be performed in order to specify the possible role of quantitative methods in the present decision processes.

2.3.3. The exploration of methods in the context of rationalizing radioprotection choices should be extended to new considerations related to various human activities involving ionizing radiations, such as :

- rationalization study of protection choices for the workers in the various light water fuel cycle power plants.
- rationalization studies of protection choices for the public which take into account the risks linked with
 - certain medical activities, such as systematic screening, use of radioelements but excluding the therapeutic exposure of patients,

- industrial activities involving use of radioisotopes
- irradiation from building materials.

These studies include the problem of assessing individual and collective doses and of identifying protection measures which can be applied in these domains. Their results should lead to the development of methods which will allow guidelines for all activities in connection with radioprotection (selection of priority sectors and determination for each case of the "ALARA" levels) to be set up.

Research on the "justification" of exposure should be associated with that on rationalization of protection choices. For this purpose the fields for which the problem of justification can be studied in a realistic way, must be identified. (the systematic tracking-down of tuberculosis seems to be one of those fields).

In the first instance, the methodology adapted to the problem of justification should be studied starting from comparative case studies showing how these aspects are usually handled in similar domains, for instance the systematic vaccination in the context of medical prevention.

